Industria y
SUPERINT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111939- -00000-0000
Fecha: 2012-07-04 16:58:07 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 4

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** INHIBIDORES DEL VIRUS DE LA HEPATITIS C

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL-MYERS-SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D. C.,** JULIO 04, 2012

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111939- -00000-0000
Fecha: 2012-07-04 16:58:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 4

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE :

(1)

X	Patente de Invención		Patente de Modelo de Utilidad
X	Capítulo I.		Capítulo II.

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: Route 206 and Province Line Road
Princeton, New Jersey 08543-4000, U.S.A.

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual _____

Número _____

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakermckenzie.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual _____

Número 79.143.366 Usaquén TP 20281

(4) INVENTOR (ES) (72)

Nombre: BELEMA, Makonen; ROMINE, Jeffrey, Lee; NGUYEN, Van, N.; WANG, Gan; LOPEZ, Omar, D.; ST. LAURENT, Denis, R.; CHEN, Qi; BENDER, John, A.; YANG, Zhong; HEWAWASAM, Piyasena; XU, Ningning; MEANWELL, Nicholas, A.; EASTER, John, A.; SU, Bao-Ning; SMITH, Michael, J.

Dirección: c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); 50 Forest Street Apt. 1710 Stamford, CT 06901 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); 14 Greyhound Court Kendall Park, NJ 08824 (US); c/o Bristol-Myers Squibb Company 1 Squibb Drive New Brunswick, NJ 08903 (US)

Nacionalidad o Domicilio: Estados unidos de América (Respectivamente)

(5) PCT (85)

Solicitud Internacional No.	PCT/US2010/060077	Fecha 13-12-2010
Publicación Internacional No.	WO 2011/075439	Fecha 23-06-2011

(6) Título (54) INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(7) Clasificación Internacional (51) C07D 403/14; C07D 405/14

(8) Prioridad

SI [X] NO [ ]

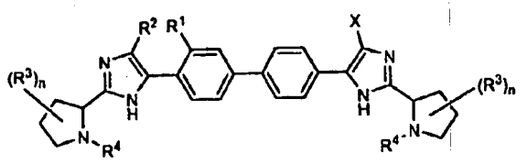
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	16-12-2009	61/286,942
US	01-12-2010	12/957,512

(9) Comprobante de pago No. 12-0062199 - 12-0049280 – 12-0049281 – 12-0049282 - **Fecha** 20-06-2012 / 17-05-2012

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [X] Documento de cesión del inventor al solicitante o a su causante
- [X] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos
  CD CON ANEXOS

11 FIGURA CARATERISTICA



(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

2012/011

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0062199

Bogotá D.C., Junio 20 de 2012 - 17:51:32

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	19870071	15/06/2012	111.555.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111939- -00000-0000
Fecha: 2012-07-04 16:58:07 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 0067245

Bogotá D.C., Julio 04 de 2012 - 16:23:40

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	49280	17/05/2012		100.000.00
RECIBO DE CA	999999999	49281	17/05/2012		100.000.00
RECIBO DE CA	999999999	49282	17/05/2012		100.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
10	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICIALES	30.000.00	300.000.00
				$300.000.00

SON: **TRESCIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
- ****** -

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-111939- -00000-0000
Fecha: 2012-07-04 16:58:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYil Eve: 378 FASENACIONALI
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Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha:	Recorrido:

Tipo de Radicación: Entrada: Salida: Traslado: Convenio:

Radicador:	Planilla:

ID	No. Radicación	Cons	Item
1			
2			
3			
4	12-111939-0		
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Item	Unidad de Conservación
1	CD
2	Disquetes
3	DVD
4	Fotos
5	Libro
6	Muestra Física
7	Otros
8	Planos
9	Periódico
10	Publicación Periódica
11	Sobre blanco tamaño carta
12	Sobre blanco tamaño oficio
13	Sobre de manila

Observaciones
Anexan CD

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud: 22) Fecha de solicitud: (30) Prioridad (31) ***No.*** (32) ***Fecha*** (33) ***País*** 61/286,942 16-12-2009 US 12/957,512 01-12-2010 US	(51) Int Cl: C07D 403/14***;*** C07D 405/14 (71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY** (72) Inventor(es) BELEMA, Makonen; ROMINE, Jeffrey, Lee; NGUYEN, Van, N.; WANG, Gan; LOPEZ, Omar, D.; ST. LAURENT, Denis, R.; CHEN, Qi; BENDER , John, A.; YANG, Zhong; HEWAWASAM, Piyasena; XU, Ningning; MEANWELL, Nicholas, A.; EASTER, John, A.; SU, Bao-Ning; SMITH, Michael, J. (74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: 16-07-2012 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 13-12-2010 No. de solicitud PCT/US2010/060077	(87) Publicación internacional Fecha: 23-06-2011 N° publicación: WO 2011/075439

(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

RESUMEN:

La presente descripción se refiere a compuestos, composiciones y métodos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se describen composiciones farmacéuticas que contienen los compuestos y métodos para usar los compuestos en el tratamiento de infección por VHC.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT _**X**_ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

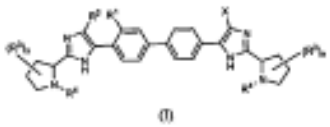
(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: C07D 403/14; C07D 405/14

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es): BELEMA, Makonen; ROMINE, Jeffrey, Lee; NGUYEN, Van, N.; WANG, Gan; LOPEZ, Omar, D.; ST. LAURENT, Denis, R.; CHEN, Qi; BENDER, John, A.; YANG, Zhong; HEWAWASAM, Piyasena; XU, Ningning; MEANWELL, Nicholas, A.; EASTER, John, A.; SU, Bao-Ning; SMITH, Michael, J.

(74) Apoderado: ALVARO CORREA ORDOÑEZ



(I)

(30) Prioridad

(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
61/286,942	16-12-2009	US
12/957,512	01-12-2010	US

(85) Fecha límite inicio fase nacional: 16-07-2012
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 13-12-2010
No. de solicitud: PCT/US2010/060077

(87) Publicación internacional:
Fecha: 23-06-2011
No. Publicación: WO 2011/075439

(54)Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(57) Resumen: La presente descripción se refiere a compuestos, composiciones y métodos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se describen composiciones farmacéuticas que contienen los compuestos y métodos para usar los compuestos en el tratamiento de infección por VHC.

CONTINUA AL RESPALDO ...

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT **X** MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: C07D 403/14; C07D 405/14

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es): BELEMA, Makonen; ROMINE, Jeffrey, Lee; NGUYEN, Van, N.; WANG, Gan; LOPEZ, Omar, D.; ST. LAURENT, Denis, R.; CHEN, Qi; BENDER, John, A.; YANG, Zhong; HEWAWASAM, Piyasena; XU, Ningning; MEANWELL, Nicholas, A.; EASTER, John, A.; SU, Bao-Ning; SMITH, Michael, J.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/286,942	16-12-2009	US
	12/957,512	01-12-2010	US

(85) Fecha inicio fase nacional: 16-07-2012

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 13-12-2010
No. de solicitud PCT/US2010/060077

(87) Publicación internacional
Fecha: 23-06-2011
N° publicación: WO 2011/075439

(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2011 (23.06.2011)

PCT

(10) International Publication Number
WO 2011/075439 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *C07D 405/14* (2006.01)

(21) International Application Number:
PCT/US2010/060077

(22) International Filing Date:
13 December 2010 (13.12.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/286,942 16 December 2009 (16.12.2009) US
12/957,512 1 December 2010 (01.12.2010) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Route 206 and ProvinceLine Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BELEMA, Makonen** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US). **ROMINE, Jeffrey, Lee** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US). **NGUYEN, Van, N.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **WANG, Gan** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **LOPEZ, Omar, D.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **ST. LAURENT, Denis, R.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **CHEN, Qi** [CN/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **BENDER, John, A.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **YANG, Zhong** [CN/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **HEWAWASAM, Piyasena** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **XU, Ningning** [CN/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **MEANWELL, Nicholas, A.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **EASTER, John, A.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **SU, Bao-Ning** [CN/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, New Jersey 08903 (US). **SMITH, Michael, J.** [US/US]; c/o Bristol-Myers Squibb Company, 1 Squibb Drive, New Brunswick, New Jersey 08903 (US).

(74) Agents: **MINGO, Pamela, A.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

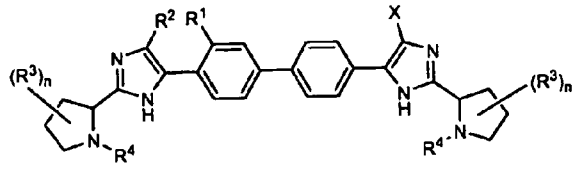
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) Title: HEPATITIS C VIRUS INHIBITORS



(I)

(57) Abstract: The present disclosure relates to compounds, compositions and methods for the treatment of Hepatitis C virus (HCV) infection. Also disclosed are pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

WO 2011/075439 A1

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial Number 61/286,942 filed December 16, 2009.

[0002] The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

[0003] HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

[0004] The current standard of care for HCV, which employs a combination of pegylated-interferon and ribavirin, has a non-optimal success rate in achieving sustained viral response and causes numerous side effects. Thus, there is a clear and long-felt need to develop effective therapies to address this undermet medical need.

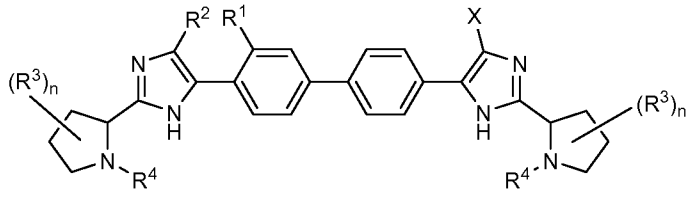
[0005] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5′ untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

[0006] Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome due to the high error rate of the encoded RNA dependent RNA polymerase which lacks a proof-reading capability. At least six major genotypes have been characterized, and more than 50 subtypes have been described with distribution worldwide. The clinical significance of the genetic heterogeneity of HCV has demonstrated a propensity for mutations to arise during monotherapy treatment, thus additional treatment options for use are desired. The possible modulator effect of genotypes on pathogenesis and therapy remains elusive.

[0007] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions by both acting as a cofactor for the NS3 protease and assisting in the membrane localization of NS3 and other viral replicase components. The formation of a NS3-NS4A complex is necessary for proper protease activity resulting in increased proteolytic efficiency of the cleavage events. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV with other HCV proteins, including NS5A, in a replicase complex.

[0008] Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in the following references: Tan, S.L. et al., *Virology*, 284:1-12 (2001); Park, K.-J. et al., *J. Biol. Chem.*, 30711-30718 (2003); Tellinghuisen, T.L. et al., *Nature*, 435:374 (2005); Love, R.A. et al., *J. Virol.*, 83:4395 (2009); Appel, N. et al., *J. Biol. Chem.*, 281:9833 (2006); Huang, L., *J. Biol. Chem.*, 280:36417 (2005); Rice, C. et al., WO 2006/093867.

[0009] In one aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

X is selected from hydrogen, alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl;

R^1 is selected from hydrogen and halo;

R^2 is selected from hydrogen, alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl; or

R^1 and R^2, together with the carbon atoms to which they are attached, form a six-membered aromatic ring optionally substituted with one halo group;

provided that at least one of X and R^2 is selected from alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl;

each R^3 is alkyl, wherein the alkyl can optionally form a fused three- or four-membered ring with an adjacent carbon atom or a spirocyclic three- or four-membered ring with the carbon atom to which it is attached; wherein the fused and spirocyclic rings are optionally substituted with one or two alkyl groups;

each R^4 is independently selected from hydrogen and $-C(O)R^5$; and

each R^5 is independently selected from alkoxy, alkyl, arylalkoxy, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

[0010] In a first embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently selected from alkoxy, heterocyclyl, and (NR^cR^d)alkyl.

[0011] In a second embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is halo. In a third embodiment of the first aspect R^2 is halo.

[0012] In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the carbon atoms to which they are attached, form a six-membered aromatic ring optionally substituted with one halo group.

[0013] In a fifth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein X is hydrogen.

[0014] In a second aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a first embodiment of the second aspect the composition further comprises at least one additional compound having anti-HCV activity. In a second embodiment of the second aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the second aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

[0015] In a fourth embodiment of the second aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0016] In a fifth embodiment of the second aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

[0017] In a third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the third aspect the method further comprises administering at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment of the third aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the third aspect the interferon is selected from

interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

[0018] In a fourth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

[0019] In a fifth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

[0020] Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

[0021] Yet other aspects and embodiments may be found in the description provided herein.

[0022] The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substituent at any given location.

[0023] It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

[0024] It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For

example, when R^1 and R^2 both contain an R^4 group, the two R^4 groups may be the same or different.

[0025] All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

[0026] As used in the present specification, the following terms have the meanings indicated:

[0027] As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

[0028] Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term "aryl".

[0029] The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

[0030] The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

[0031] The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

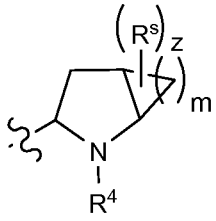
[0032] The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

[0033] The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

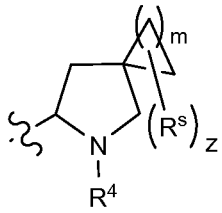
[0034] The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0035] The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

[0036] The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when R^3 is alkyl, the alkyl can optionally form a fused three- or four-membered ring with an adjacent carbon atom to provide the structure shown below:



wherein m is selected from 1 and 2, wherein z is 0, 1, or 2, and wherein R^s is alkyl; or wherein the alkyl can optionally form a spirocyclic three- or four-membered ring with the carbon atom to which it is attached to provide the structure shown below:



wherein m is selected from 1 and 2; wherein z is 0, 1, or 2, and wherein R^s is alkyl.

[0037] The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

[0038] The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

[0039] The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

[0040] The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

[0041] The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy,

haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0042] The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0043] The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0044] The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, $-NR^xR^y$, and oxo.

[0045] The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0046] The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

[0047] The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

[0048] The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

[0049] The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

[0050] The term "carbonyl," as used herein, refers to -C(O)-.

[0051] The term "carboxy," as used herein, refers to $-CO_2H$.

[0052] The term "cyano," as used herein, refers to -CN.

[0053] The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

[0054] The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

[0055] The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0056] The term "cycloalkyloxycarbonyl," as used herein, refers to a cycloalkyloxy group attached to the parent molecular moiety through a carbonyl group.

[0057] The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

[0058] The term "formyl," as used herein, refers to -CHO.

[0059] The term "halo," as used herein, refers to Cl, Br, F, or I.

[0060] The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0061] The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0062] The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

[0063] The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged

bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, and 2-azabicyclo[2.2.2]oct-3-yl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, oxetanyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, thienyl, and thiomorpholinyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0064] The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

[0065] The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

[0066] The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^cR^d$, wherein the aryl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

[0067] The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0068] The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

[0069] The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

[0070] The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

[0071] The term "hydroxy," as used herein, refers to -OH.

[0072] The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

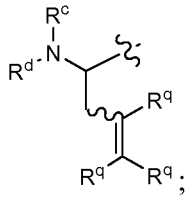
[0073] The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

[0074] The term "nitro," as used herein, refers to $-NO_2$.

[0075] The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkyloxy, cycloalkyloxycarbonyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR′, and $-C(NCN)NR^xR^y$, wherein R′ is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three

substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0076] The term "(NR^cR^d)alkenyl," as used herein, refers to



wherein R^c and R^d are as defined herein and each R^q is independently hydrogen or C_{1-3} alkyl.

[0077] The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^d$ groups. The alkyl part of the (NR^cR^d)alkyl is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfanyl, arylalkoxycarbonyl, carboxy, cycloalkyl, heterocyclyl, heterocyclylcarbonyl, hydroxy, and (NR^eR^f)carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

[0078] The term "$-NR^eR^f$," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

[0079] The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^eR^f$ groups.

[0080] The term "(NR^eR^f)alkylcarbonyl," as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

[0081] The term "(NR^eR^f)carbonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a carbonyl group.

[0082] The term "(NR^eR^f)sulfonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a sulfonyl group.

[0083] The term "$-NR^xR^y$," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are

independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{x'}R^{y'}$)carbonyl, wherein $R^{x'}$ and $R^{y'}$ are independently selected from hydrogen and alkyl.

[0084] The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

[0085] The term "(NR^xR^y)carbonyl," as used herein, refers to an -NR^xR^y group attached to the parent molecular moiety through a carbonyl group.

[0086] The term "-NR^xR^y," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen and alkyl.

[0087] The term "($NR^{x'}R^{y'}$)carbonyl," as used herein, refers to an -$NR^{x'}R^{y'}$ group attached to the parent molecular moiety through a carbonyl group.

[0088] The term "oxo," as used herein, refers to =O.

[0089] The term "sulfonyl," as used herein, refers to -SO_2-.

[0090] Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

[0091] Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

[0092] The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

[0093] The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

[0094] The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

[0095] The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate,

trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

[0096] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N′-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0097] When it is possible that, for use in therapy, therapeutically effective amounts of a compound of Formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of Formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, *e.g.*, a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the

other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0098] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford anti-virally effective results without causing any harmful or deleterious side effects.

[0099] When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at

dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

[00100] Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

[00101] Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

[00102] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

[00103] Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

[00104] Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in

these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

[00105] Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

[00106] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

[00107] The compounds of Formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

[00108] The compounds of Formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[00109] Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6):318 (1986).

[00110] Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

[00111] For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

[00112] Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

[00113] Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

[00114] Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

[00115] Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

[00116] Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

[00117] Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

[00118] Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

[00119] It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[00120] The term "patient" includes both human and other mammals.

[00121] The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or

condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or condition, *i.e.*, causing regression of the disease, disorder, and/or condition.

[00122] The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology*, 38:1282 (2003); *Biochem. Biophys. Res. Commun.*, 313:42 (2004); *J. Gastroenterol.*, 38:567 (2003)).

[00123] Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
NIM811 Debio-025		Cyclophilin inhibitors	Novartis Debiopharm
Zadaxin		Immunomodulator	SciClone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-Tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV inhibitor	Achillion / Gilead

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Pyrazolopyrimidine compounds and salts From WO 2005/047288 26 May 2005	Antiviral	HCV inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	Monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B replicase inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B replicase inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B replicase inhibitor	Gene Labs / Novartis
2′C MeA	Antiviral	NS5B replicase inhibitor	Gilead
PSI 6130	Antiviral	NS5B replicase inhibitor	Roche

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
R1626	Antiviral	NS5B replicase inhibitor	Roche
2′C Methyl adenosine	Antiviral	NS5B replicase inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	Ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	Ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	Ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	Serine protease inhibitor	Schering-Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	Immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
CELLCEPT®	Immunosuppressant	HCV IgG immuno-suppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immuno-suppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	Albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
REBIF®	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche Ltd., Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharma. Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b / ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen / Valentis
Wellferon	Interferon	Lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a / immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a / ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b / ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	Antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	Caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B replicase inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
Boceprevir	Antiviral	Serine protease inhibitor	Schering-Plough
TMS-435	Antiviral	Serine protease inhibitor	Tibotec BVBA, Mechelen, Belgium
BI-201335	Antiviral	Serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
MK-7009	Antiviral	Serine protease inhibitor	Merck
PF-00868554	Antiviral	Replicase inhibitor	Pfizer
ANA598	Antiviral	Non-Nucleoside NS5B polymerase inhibitor	Anadys Pharmaceuticals, Inc., San Diego, CA, USA

Brand Name	Physiological Class	Type of Inhibitor or Target	Source Company
IDX375	Antiviral	Non-Nucleoside replicase inhibitor	Idenix Pharmaceuticals, Cambridge, MA, USA
BILB 1941	Antiviral	NS5B polymerase inhibitor	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada
PSI-7851	Antiviral	Nucleoside polymerase inhibitor	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	NS5B polymerase inhibitor	Vir °Chem Pharma
VCH-916	Antiviral	NS5B polymerase inhibitor	Vir °Chem Pharma
GS-9190	Antiviral	NS5B polymerase inhibitor	Gilead
Peg-interferon lamda	Antiviral	Interferon	ZymoGenetics / Bristol-Myers Squibb

[00124] The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

[00125] The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, *e.g.*, blood, tissue,

surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

[00126] This disclosure is intended to encompass compounds having Formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

[00127] The abbreviations used in the present application, including particularly in the illustrative examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: ca. for about; min or mins for minutes; h or hr or hrs for hours; rt or RT for room temperature or retention time (context will dictate); R_t for retention time; TFA for trifluoroacetic acid; DMSO for dimethylsulfoxide; Me for methyl; THF for tetrahydrofuran; *t*-Bu or *t*-Bu for *tert*-butyl; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; DBU for 1,8-diazabicycloundec-7-ene; Ph for phenyl; DEA for diethylamine; Et for ethyl; DMF for N,N-dimethylformamide; OAc for acetate; HMDS for hexamethyldisilane; pTsOH for para-toluenesulfonic acid; iPr_2EtN, DIEA, or DIPEA for diisopropylethylamine; EtOAc or EtOAc or EA for ethyl acetate; Et_3SiH for triethylsilane; MeOH for methanol; $TMSCHN_2$ for trimethylsilyldiazomethane; H-D-Ser-OBzl.HCl for D-serine benzyl ester hydrochloride; EtOH for ethanol; Me_2S for dimethylsulfide; TEA or Et_3N for triethylamine; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutylaluminum hydride; TBDMS-Cl for *tert*-butyldimethylsilyl chloride; i-PrOH for isopropanol; Boc, boc, or BOC for *tert*-butoxycarbonyl; Cbz-Cl for benzyl chloroformate; Bn for benzyl; DEAD for diethylazodicarboxylate; mCPBA for meta-chloroperoxybenzoic acid; DCM for dichloromethane; TMSCN for trimethylsilyl cyanide; ACN or MECN for acetonitrile; dpppe for 1,5-bis(diphenylphosphino)pentane; TMEDA for tetramethylethylenediamine; DMA for N,N-dimethylacetamide; MeOD for CD_3OD; Hex for hexanes; NaOEt for sodium ethoxide; MTBE for methyl tert butyl ether; NCS for N-chlorosuccinimide; Et_2O for diethyl ether; DME for 1,2-dimethoxyethane; and EEDQ for N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.

[00128] The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included

within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

[00129] Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art.

SYNTHESIS OF COMMON CAPS

Compound Analysis Conditions

[00130] Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters MICROMASS® ZQ MS system. It should be noted that retention times may vary slightly between machines. Additional LC conditions applicable to the current section, unless noted otherwise.

Cond.-MS-W1

Column = XTERRA® 3.0 X 50 mm S7
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-MS-W2

Column = XTERRA® 3.0 X 50 mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min

Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-MS-W5
Column = XTERRA® 3.0 X 50 mm S7
Start %B = 0
Final %B = 30
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-D1
Column = XTERRA® C18 3.0 X 50 mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-D2
Column = PHENOMENEX® Luna 4.6 X 50 mm S10
Start %B = 0
Final %B = 100

Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-M3
Column = XTERRA® C18 3.0 X 50 mm S7
Start %B = 0
Final %B = 40
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

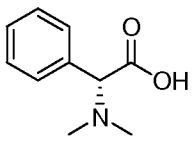
Condition I
Column = PHENOMENEX® Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition II
Column = PHENOMENEX® Luna 4.6 X 50 mm S10
Start %B = 0

Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition III
Column = XTERRA® C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cap-1

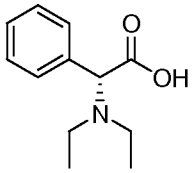


(R)-2-(Dimethylamino)-2-phenylacetic acid

[00131] A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (CELITE®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of Cap-1 as a white needle (4.0 g). Optical rotation: -117.1° [c=9.95 mg/mL in H_2O; λ=589 nm]. ^1H NMR (DMSO-d_6, δ=2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Condition I): RT=0.25; LC-MS:

Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

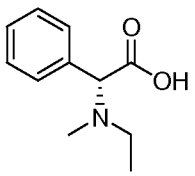
Cap-2



(R)-2-(Diethylamino)-2-phenylacetic acid

[00132] $NaBH_3CN$ (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and methanol (100 mL), and stirred for 5 minutes. Acetaldehyde (10 mL) was added dropwise over 10 minutes and stirring was continued at the same cooled temperature for 45 minutes and at ambient temperature for ~6.5 hours. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a dropwise addition of concentrated HCl over ~ 45 minutes until the pH of the mixture was ~ 1.5 - 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred overnight, filtered to remove the white suspension, and the filtrate was concentrated *in vacuo*. The crude material was recrystallized from ethanol to afford the HCl salt of Cap-2 as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). ^1H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c=0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c=0.357, H_2O). LC (Condition I): RT=0.43 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26.

Cap-3

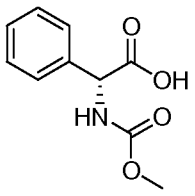


[00133] Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-

2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H_2 for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under H_2 atmosphere for 24 hours [Note: the supply of H_2 was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (CELITE®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). ^{1}H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, *J*=7.2, 3H). LC (Condition I): RT=0.39 min; >95 % homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

[00134] A suspension of 10% Pd/C (536 mg) in methanol/H_2O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H_2 for ~72 hours, where the H_2 supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (CELITE®) and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of Cap-3 as a white solid (985 mg). ^{1}H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Condition I): RT=0.39 min; >95 % homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

Cap-4



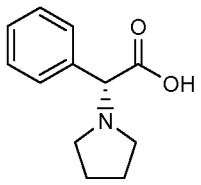
(R)-2-(Methoxycarbonylamino)-2-phenylacetic acid

[00135] $ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-*tert*-butyl 2-amino-2-phenylacetate/HCl (9.877 g,

40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-*tert*-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). ^1H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): 7.98 (d, *J*=8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, *J*=8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Condition I): RT=1.53 min; ~90 % homogeneity index; LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

[00136] TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed *in vacuo*, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried *in vacuo* to provide Cap-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c=3.7 mg/mL in H_2O; λ=589 nm]. ^1H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, *J*=8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, *J*=8.3, 1H), 3.55 (s, 3H). LC (Condition I): RT=1.01 min; >95 % homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

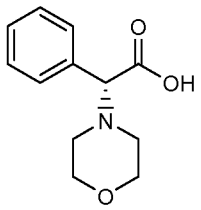
Cap-5



[00137] A mixture of (R)-2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and

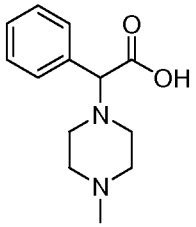
filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed *in vacuo*. The resulting crude material was purified by a reverse phase HPLC (water/methanol/TFA) to provide the TFA salt of Cap-5 as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT=0.30 minutes (Condition I); >98% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

Cap-6



[00138] The TFA salt of Cap-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of Cap-5. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT=0.32 minutes (Condition I); >98%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

Cap-7



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

[00139] A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a

freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^1H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 7.78 (d, *J*= 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, *J*=12.5, 1H), 5.10 (d, *J*=12.5, 1H), 2.39 (s, 3H). RT=3.00 (Condition III); >90% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

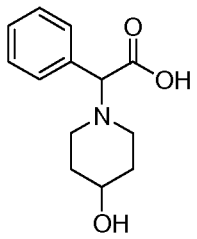
[00140] A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (CHIRALCEL® OD-H) indicated that the sample is a mixture of stereoisomers in a 38.2 to 58.7 ratio. The separation of the stereoisomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Stereoisomer-1 (1.474 g) and stereoisomer-2 (2.2149 g) were retrieved as viscous oil. ^1H NMR ($CDCl_3$, δ=7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, *J*=12.5, 1H), 5.08 (d, *J*=12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT=2.10 (Condition III); >98% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

[00141] A methanol (10 mL) solution of either stereoisomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 minutes. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth

(CELITE®) and the filtrate was concentrated *in vacuo* to provide Cap-7, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield). The product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. br s, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT=0.31 (Condition II); >90% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.

[00142] The synthesis of Cap-8 and Cap-9 was conducted according to the synthesis of Cap-7 by using appropriate amines for the SN_2 displacement step (*i.e.*, 4-hydroxypiperidine for Cap-8 and (S)-3-fluoropyrrolidine for Cap-9) and modified conditions for the separation of the respective stereoisomeric intermediates, as described below.

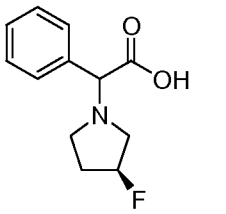
Cap-8



8a: enantiomer-1
8b: enantiomer-2

[00143] The stereoisomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of stereoisomer-1 and 209.1 mg of stereoisomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of Cap-7 to provide Cap-8: ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) 7.40 (d, *J*=7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT=0.28 (Condition II); >98% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

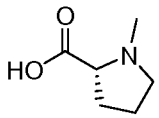
Cap-9



9a: diastereomer-1
9b: diastereomer-2

[00144] The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereoisomers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Cap-9a and Cap-9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA solvent): ^1H NMR (DMSO-d_6, δ=2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J*=53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT=0.42 (Condition I); >95% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; Cap-9b (diastereomer-2): ^1H NMR (DMSO-d_6, δ=2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J*=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Condition I); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

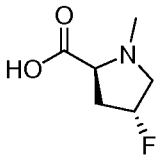
Cap-10



[00145] To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (CELITE®) and concentrated

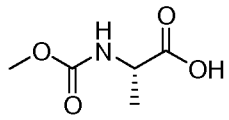
in vacuo to provide Cap-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J*=9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT=0.28 (Condition II); >98% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



[00146] A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (CELITE®) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of Cap-11 as a white solid (337.7 mg). ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) 5.39 (d m, *J*=53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J*=31.5, 13.5, 4.5, 1H), 3.33 (dd, *J*=25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT=0.28 (Condition II); >98% homogeneity index; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

Cap-12 (same as Cap-52)

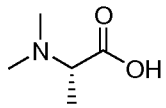


(S)-2-(Methoxycarbonylamino)propanoic acid

[00147] L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was

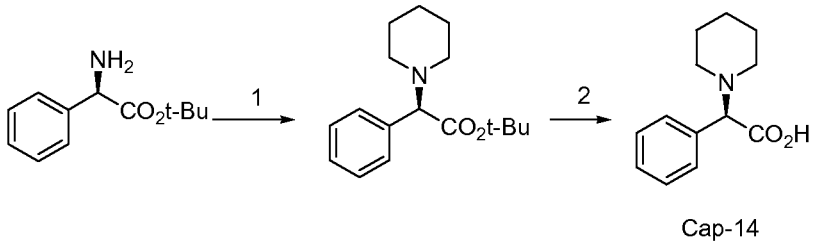
purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of Cap-12 as a colorless oil. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) 7.44 (d, *J*=7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J*=7.3, 3H).

Cap-13



[00148] A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (CELITE®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ=2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J*=7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J*=7.3, 3H).

Cap-14



Cap-14

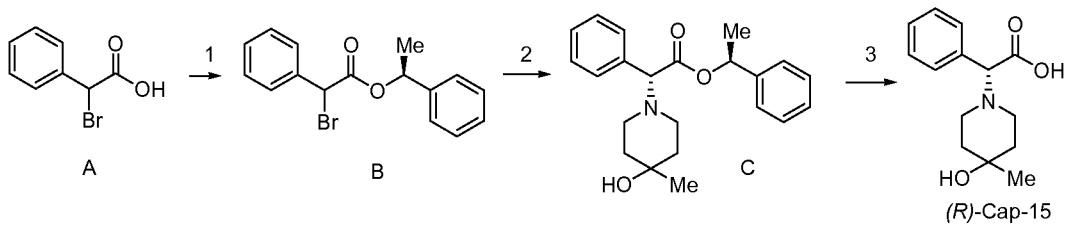
(R)-2-Phenyl-2-(piperidin-1-yl)acetic acid

[00149] Step 1: A mixture of (R)-(-)-D-phenylglycine *tert*-butyl ester (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x

100mm; CH_3CN-H_2O-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, *J*=10.9 Hz, 1H), 3.59 (d, *J*=10.9 Hz, 1H), 2.99 (t, *J*=11.2 Hz, 1H), 2.59 (t, *J*=11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, *J*=1.82 Hz, 3H), 1.40 (s, 9H). LC-MS: Anal. Calcd. for $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

[00150] Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ^1H NMR (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC-MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



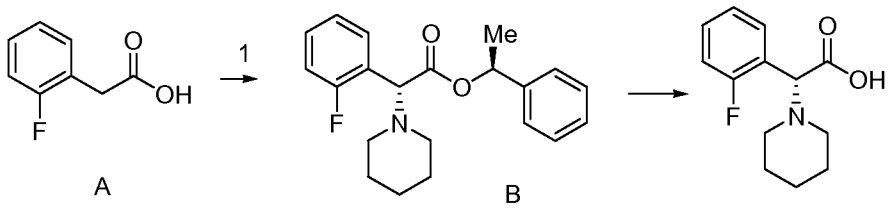
[00151] Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate. To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H_2O x 2, brine), dried (Na_2SO_4), filtered, and concentrated to give a pale yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound

(11.64 g, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, *J*=6.6 Hz, 0.5H), 5.94 (q, *J*=6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, *J*=6.6 Hz, 1.5H), 1.51 (d, *J*=6.6 Hz, 1.5H).

[00152] Step 2: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate. To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^{1}H NMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, *J*=6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, *J*=6.6 Hz, 3H), 1.18 (s, 3H). LC-MS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}H NMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, *J*=6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, *J*=6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, *J*=6.8 Hz, 3H), 1.20 (s, 3H). LC-MS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

[00153] Step 3: (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid. To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish solid (0,128 g, 98%). LC-MS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



A B *(R)*-Cap-16

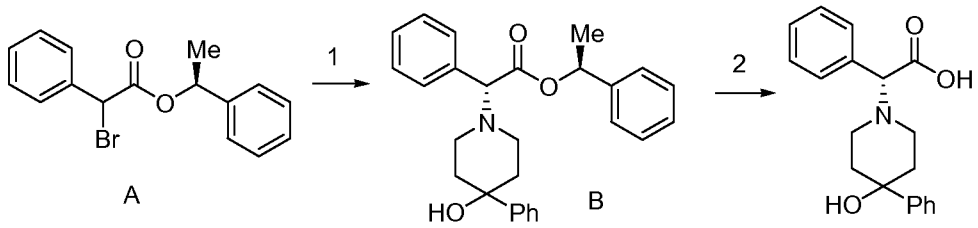
[00154] Step 1: (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate. A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BIOTAGE®/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, *J*=6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, *J*=6.5 Hz, 3H).

[00155] Step 2: (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate. To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0 °C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica gel chromatography (BIOTAGE®/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ^{1}H NMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (BIOTAGE®/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ^{1}H NMR (400

MHz, CD_3OD) δ 7.52 (ddd, *J*=9.4, 7.6, 1.8 Hz, 1H), 7.33 - 7.40 (m, 1), 7.23 - 7.23 (m, 4H), 7.02 - 7.23 (m, 4H), 5.86 (q, *J*=6.6 Hz, 1H), 4.45 (s, 1H), 2.39 - 2.45 (m, 4H), 1.52 - 1.58 (m, 4H), 1.40 - 1.42 (m, 1H), 1.38 (d, *J*=6.6 Hz, 3H). LC-MS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

[00156] Step 3: (R)-2-(2-Fluorophenyl)-2-(piperidin-1-yl)acetic acid. A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (CELITE®), and concentrated *in vacuo*. This provided the title compound as a colorless solid (0.503 g, 98%). ^1H NMR (400 MHz, CD_3OD) δ 7.65 (ddd, *J*=9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LC-MS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

Cap-17

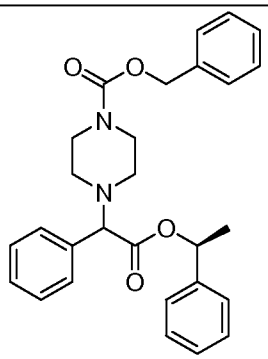


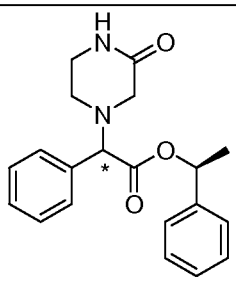
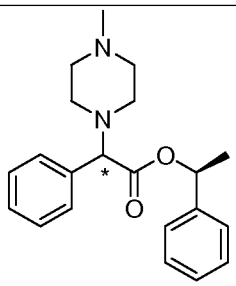
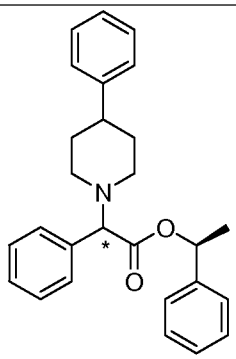
(R)-Cap-17

[00157] Step 1: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate. To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^1H NMR. Separation of these isomers was performed using supercritical fluid chromatography (CHIRALCEL® OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the

corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, *J*=11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, *J*=11.1, 2.5 Hz, 1H), 2.20 (dt, *J*=12.1, 4.6 Hz, 1H), 2.10 (dt, *J*=12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, *J*=6.5 Hz, 3H). LC-MS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: H^{1}NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, *J*=11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, *J*=11.1, 2.5 Hz, 1H), 2.25 (dt, *J*=12.1, 4.6 Hz, 1H), 2.12 (dt, *J*=12.1, 4.6 Hz, 1H), 1.73 (dd, *J*=13.6, 3.0 Hz, 1H), 1.64 (dd, *J*=13.6, 3.0 Hz, 1H), 1.40 (d, *J*=6.6 Hz, 3H). LC-MS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

[00158] The following esters were prepared in similar fashion:

Intermediate-17a		Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23-2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15-7.52 (m, 15H). LC-MS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; found: 459.44 $(M+H)^+$. Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27-2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19-7.27 (m, 3H) 7.27-7.44 (m, 10H). LC-MS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; found: 459.44 $(M+H)^+$.

Intermediate -17b		Diastereomer 1: RT=11.76 minutes (Condition II); LC-MS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16; found: 339.39 $(M+H)^+$. Diastereomer 2: RT=10.05 minutes (Condition II). LC-MS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16; found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: T_R=4.55 minutes (Condition I); LC-MS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20; found: 339.45 $(M+H)^+$. Diastereomer 2: T_R=6.00 minutes (Condition I). LC-MS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20; found: 339.45 $(M+H)^+$.
Intermediate -17d		Diastereomer 1: RT=7.19 minutes (Condition I); LC-MS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22; found: 400.48 $(M+H)^+$. Diastereomer 2: RT=9.76 minutes (Condition I); LC-MS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22; found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time:

Condition I

Column: CHIRALPAK® AD-H Column, 4.62x50 mm, 5µm

Solvents: 90% CO_2-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored at 220 nm

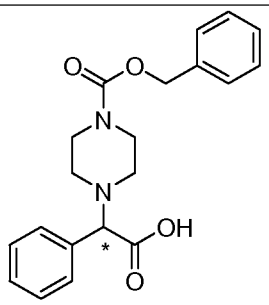
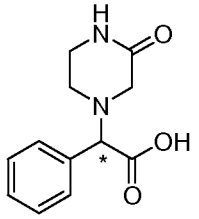
Injection: 1.0 mg/3mL methanol

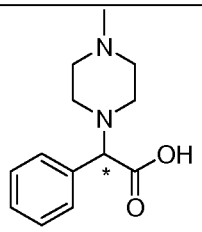
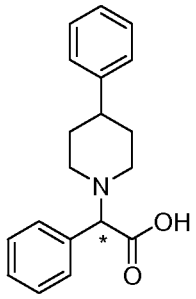
Condition II

Column: CHIRALCEL® OD-H Column, 4.62x50 mm, 5μm
Solvents: 90% CO_2-10% methanol with 0.1%DEA
Temp: 35 °C
Pressure: 150 bar
Flow rate: 2.0 mL/min.
UV monitored at 220 nm
Injection: 1.0 mg/mL methanol

[00159] Cap-17, Step 2: (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid. To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LC-MS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311.15; found: 312 $(M+H)^+$.

[00160] The following carboxylic acids were prepared in optically pure form in a similar fashion:

Cap-17a		RT=2.21 (Condition II); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20-2.35 (m, 2H) 2.34-2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06-7.53 (m, 10H). LC-MS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.16; found: 355.38 $(M+H)^+$.
Cap-17b		RT=0.27 (Condition III); LC-MS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.10; found: 235.22 $(M+H)^+$.

Cap-17c		RT=0.48 (Condition II); LC-MS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.14; found: 235.31 $(M+H)^+$.
Cap-17d		RT=2.21 (Condition I); LC-MS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.16; found: 296.33 $(M+H)^+$.

LC-MS Conditions for determining retention time:

Condition I

Column: PHENOMENEX® Luna 4.6 X 50 mm S10

Start % B=0

Final % B=100

Gradient Time=4 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol - 90% H_2O - 0.1% TFA

Solvent B=90% methanol - 10% H_2O - 0.1% TFA

Condition II

Column: Waters SunFire 4.6 X 50 mm S5

Start % B=0

Final % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol - 90% H_2O - 0.1% TFA

Solvent B=90% methanol - 10% H_2O - 0.1% TFA

Condition III

Column: PHENOMENEX® 10µ 3.0 X 50 mm

Start % B=0

Final % B=100

Gradient Time=2 min

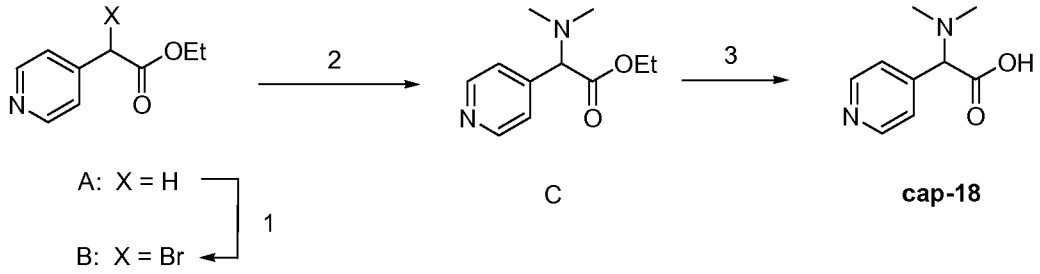
Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol - 90% H_2O - 0.1% TFA

Solvent B=90% methanol - 10% H_2O - 0.1% TFA

Cap-18

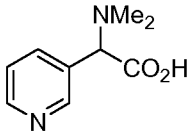
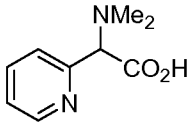
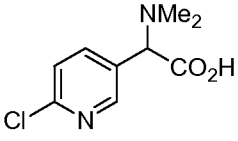


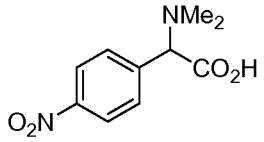
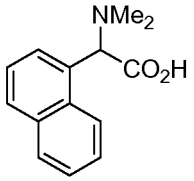
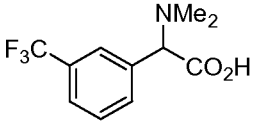
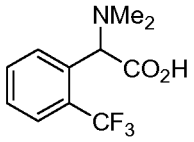
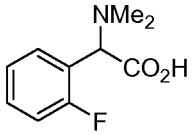
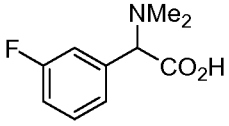
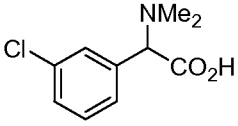
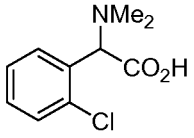
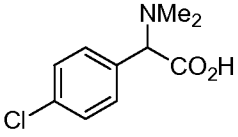
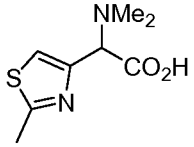
[00161] Step 1: (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate. To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J*=4.6, 1.8 Hz, 2H), 7.45 (dd, *J*=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H). LC-MS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

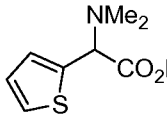
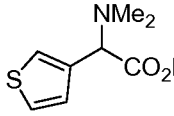
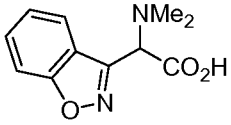
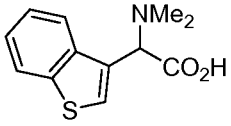
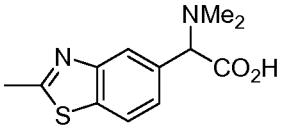
[00162] Step 2: (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate. To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (BIOTAGE®, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J*=6.0 Hz, 2H), 7.36 (d, *J*=6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, *J*=7.0 Hz). LC-MS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

[00163] Step 3: (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid. To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g, 4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J*=5.7 Hz, 2H), 7.34 (d, *J*=5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

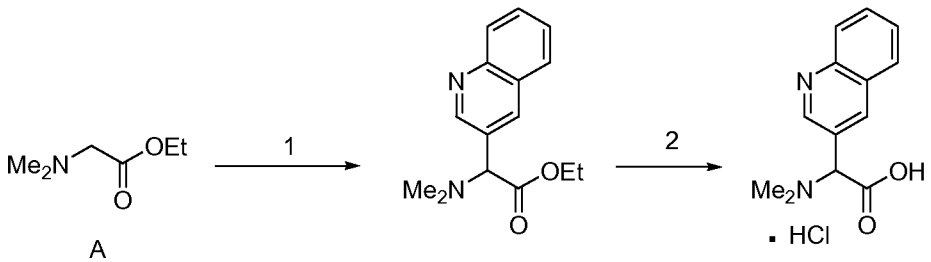
[00164] The following examples were prepared in similar fashion using the method described above:

Cap-19		LC-MS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LC-MS: no ionization. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, *J*=4.3 Hz, 1H), 7.84 (app t, *J*=5.3 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.37 (app t, *J*=5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LC-MS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.

Cap-22		LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LC-MS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 229; found: 230 $(M+H)^+$.
Cap-24		LC-MS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-25		LC-MS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LC-MS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.
Cap-27		LC-MS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LC-MS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-29		LC-MS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-30		LC-MS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-31		LC-MS: Anal. Calcd. for $C_8H_{12}N_2O_2S$: 200; found: 201 $(M+H)^+$.

Cap-32		LC-MS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LC-MS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LC-MS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.
Cap-35		LC-MS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.
Cap-36		LC-MS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

Cap-37



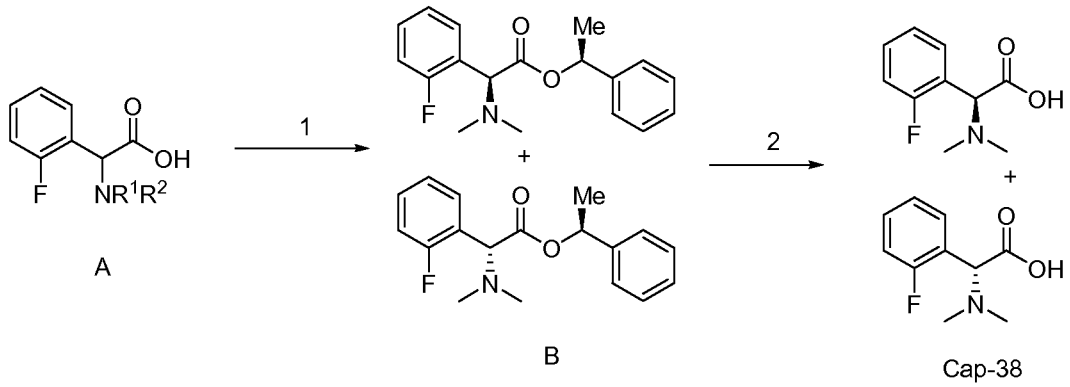
A B cap-37

[00165] Step 1: (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate. A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol), 3-bromoquinoline and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into H_2O. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) and then by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J*=2.0 Hz, 1H), 8.32 (d, *J*=2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, *J*=7.0 Hz, 3H). LC-MS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 $(M+H)^+$.

[00166] Step 2: (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid. A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LC-MS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

Cap-38



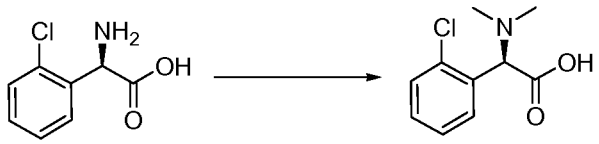
[00167] Step 1: (R)-((S)-1-Phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-Phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate. To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed *in vacuo* and the residue partitioned with ethyl acetate-H_2O. The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BIOTAGE®/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give first (S)-1-

phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g. 18%), both as their TFA salts. (S,R)-isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 7.65-7.70 (m, 1H), 7.55-7.60 (ddd, *J*=9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, *J*=6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, *J*=6.5 Hz, 3H). LC-MS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$; (S,S)-isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, *J*=8.5, 1.5 Hz, 2H), 6.02 (q, *J*=6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, *J*=6.5 Hz, 3H). LC-MS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

[00168] Step 2: (R)-2-(Dimethylamino)-2-(2-fluorophenyl)acetic acid. A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (CELITE®), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LC-MS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

[00169] The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

Cap-39

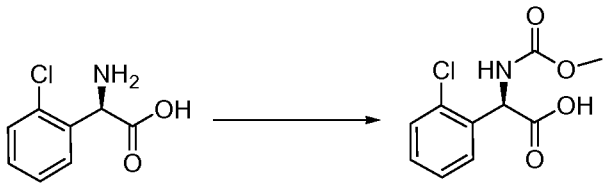


cap-39

[00170] A mixture of (R)-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (CELITE®) and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the TFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil

(0.290 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LC-MS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.

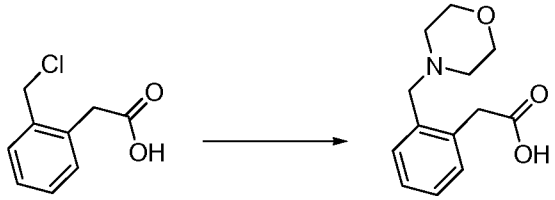
Cap-40



cap-40

[00171] To an ice-cold solution of (R)-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H_2O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 - 7.43 (m, 2H), 7.29 - 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LC-MS: Anal. Calcd. for $C_{10}H_{10}ClNO_4$: 243; found: 244 $(M+H)^+$.

Cap-41

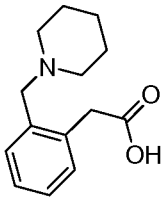
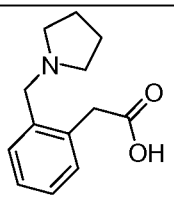
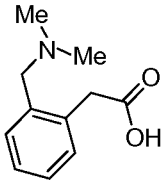
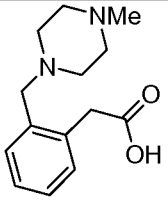


cap-41

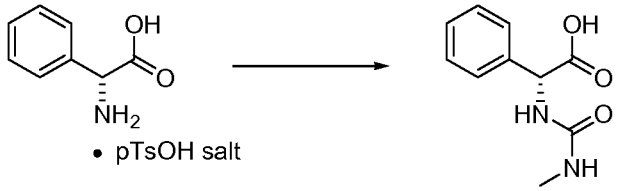
[00172] To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (BIOTAGE®/ 0-10% methanol-CH_2Cl_2) to give the title compound 2-(2-(morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g,

87%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LC-MS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

[00173] The following examples were similarly prepared using the method described for Cap-41:

Cap-42		LC-MS: Anal. Calcd. for $C_{14}H_{19}NO_2$: 233; found: 234 $(M+H)^+$.
Cap-43		LC-MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.
Cap-44		LC-MS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 194 $(M+H)^+$.
Cap-45		LC-MS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

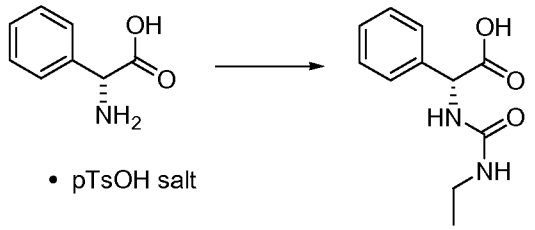
Cap-45a



Cap-45a

[00174] HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26-7.38 (m, 5H) 12.67 (s, 1H). LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; HPLC PHENOMENEX® C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.38 min, 90% homogeneity index.

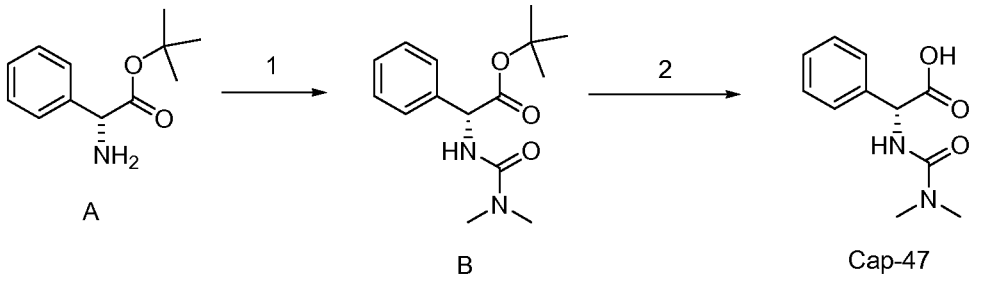
Cap-46



cap-46

[00175] The desired product was prepared according to the method described for Cap-45a. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94-3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26-7.38 (m, 5H) 12.68 (s, 1H). LC-MS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$ 222.10 found 223.15 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=0.87 min, 90% homogeneity index.

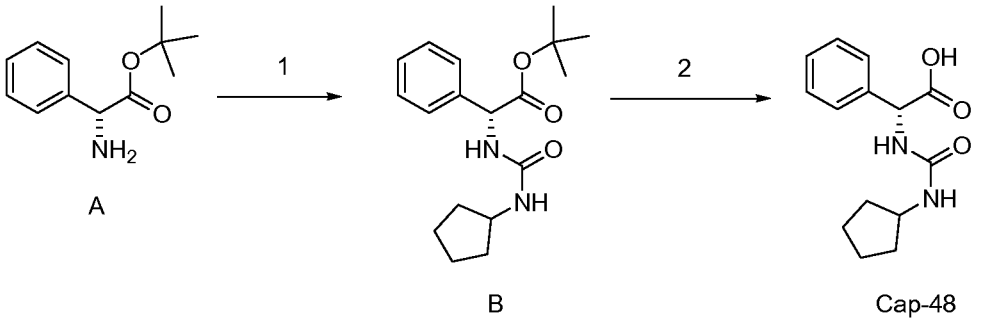
Cap-47



[00176] Step 1: (R)-*tert*-Butyl 2-(3,3-dimethylureido)-2-phenylacetate. To a stirred solution of (R)-*tert*-butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-*tert*-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, *J*=7.63 Hz, 1H) 6.55 (d, *J*=7.32 Hz, 1H) 7.24-7.41 (m, 5H). LC-MS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC PHENOMENEX® Luna C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.26 min, 97% homogeneity index.

[00177] Step 2: (R)-2-(3,3-Dimethylureido)-2-phenylacetic acid. To a stirred solution of ((R)-*tert*-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 hours. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LC-MS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=0.75 min, 93% homogeneity index.

Cap-48

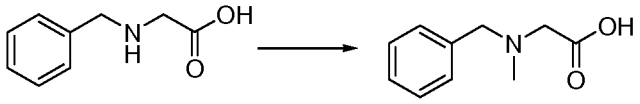


[00178] Step 1: (R)-*tert*-Butyl 2-(3-cyclopentylureido)-2-phenylacetate. To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. (R)-*tert*-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. ^{1}H NMR (500 MHz, CD_3Cl-D) δ ppm 1.50-1.57 (m, 2H) 1.58-1.66 (m, 2H) 1.87-1.97 (m, 2H) 3.89-3.98 (m, 1H) 5.37 (s, 1H) 7.26-7.38 (m, 5H). LC-MS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA® C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.82 min, 96% homogeneity index.

[00179] Step 2: (R)-2-(3-Cyclopentylureido)-2-phenylacetic acid. To a stirred solution of (R)-*tert*-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH_2Cl_2 (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17-1.35 (m, 2H) 1.42-1.52 (m, 2H) 1.53-1.64 (m, 2H) 1.67-1.80 (m, 2H) 3.75-3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24-7.40

(m, 5H) 12.73 (s, 1H). LC-MS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$: 262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=1.24 min, 100% homogeneity index.

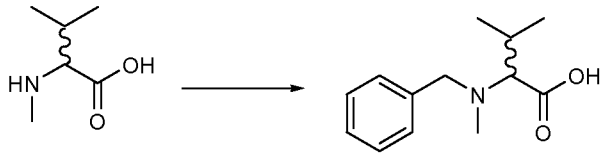
Cap-49



cap-49

[00180] To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (XTERRA® 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LC-MS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.09; found: 180.20 $(M+H)^+$.

Cap-50

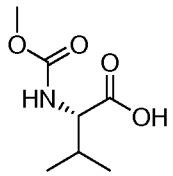


Cap-50

[00181] To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified

by reverse-phase preparative HPLC (XTERRA® 30 x 100mm, detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33-2.48 (m, 1H) 2.54-2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29-7.65 (m, 5H). LC-MS: Anal. Calcd. for: $C_{13}H_{19}NO_2$ 221.14; found: 222.28 $(M+H)^+$.

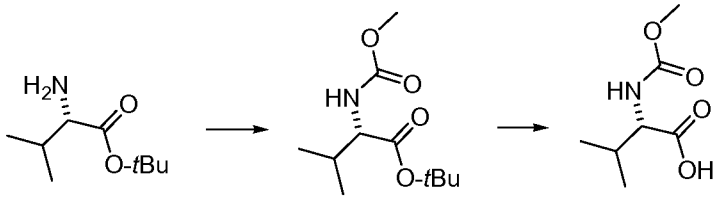
Cap-51



(S)-2-(Methoxycarbonylamino)-3-methylbutanoic acid

[00182] Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ=2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, *J*=8.6, 1H), 3.84 (dd, *J*=8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922.

Cap-51 (alternate route)



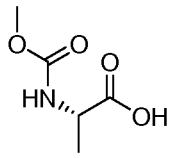
(S)-2-(Methoxycarbonylamino)-3-methylbutanoic acid

[00183] DIEA (137.5 mL, 0.766 mol) was added to a suspension of (*S*)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride (75.0 g, 0.357 mol) in THF (900 mL), and the mixture was cooled to 0 °C (ice/water bath). Methyl chloroformate (29.0 mL, 0.375 mol) was added dropwise over 45 min, the cooling bath was removed and the heterogeneous mixture was stirred at ambient temperature for 3 h. The solvent was removed under diminished pressure and the residue partitioned between EtOAc and water (1 L each). The organic layer was washed with H_2O (1 L) and brine (1 L), dried ($MgSO_4$), filtered and concentrated under diminished pressure. The crude material was passed through a plug of silica gel (1 kg), eluting with hexanes (4 L) and 15:85 EtOAc/hexanes (4 L) to afford (S)-*tert*-butyl 2-(methoxycarbonylamino)-3-methylbutanoate as a clear oil (82.0 g, 99% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ = 2.5 ppm) 7.34 (d, J = 8.6, 1 H), 3.77 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.05 (m, 1 H), 1.39 (s, 9 H), 0.83 - 0.92 (m, 6 H). ^{13}C-NMR (126 MHz, DMSO-d_6, δ = 39.2 ppm) 170.92, 156.84, 80.38, 60.00, 51.34, 29.76, 27.62, 18.92, 17.95. LC-MS: $[M+Na]^+$ 254.17.

[00184] Trifluoroacetic acid (343 mL, 4.62 mol) and Et_3SiH (142 mL, 0.887 mol) were added sequentially to a solution of (S)-*tert*-butyl 2-(methoxycarbonylamino)-3-methylbutanoate (82.0 g, 0.355 mol) in CH_2Cl_2 (675 mL), and the mixture was stirred at ambient temperature for 4 h. The volatile component was removed under diminished pressure and the resultant oil triturated with petroleum ether (600 mL) to afford a white solid, which was filtered and washed with hexanes (500 mL) and petroleum ether (500 mL). Recrystallization from EtOAc/petroleum ether afforded Cap-51 as white flaky crystals (54.8 g, 88 % yield). MP = 108.5-109.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, J = 8.6, 1 H), 3.83 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, J = 8.9, 7.0, 6 H). ^{13}C NMR (126 MHz, DMSO-d_6, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98. LC-MS: $[M+H]^+$ = 176.11. Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 48.17; H, 7.55; N, 7.99. Optical Rotation: $[\alpha]_D$ = -4.16 (12.02 mg/mL; MeOH). Optical purity: >99.5 % ee. Note: the optical purity assessment was made on the methyl ester derivative of Cap-51, which was prepared under a standard $TMSCHN_2$ (benzene/MeOH) esterification protocol. HPLC analytical conditions: column, CHIRALPAK® AD-H (4.6 x 250mm, 5μm); solvent, 95% heptane / 5% IPA (isocratic); flow rate, 1 mL/min; temperature, 35 °C; UV monitored at 205 nm.

[Note: Cap-51 could also be purchased from Flamm.]

Cap-52 (same as Cap-12)

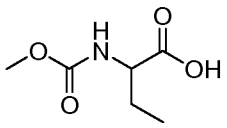


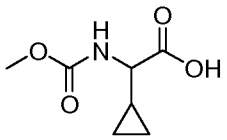
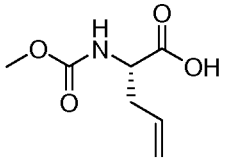
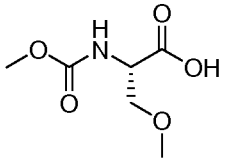
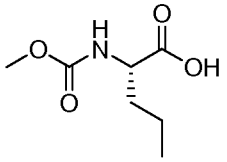
(S)-2-(Methoxycarbonylamino)propanoic acid

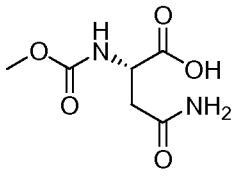
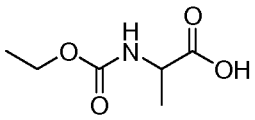
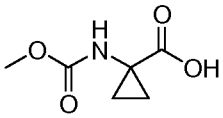
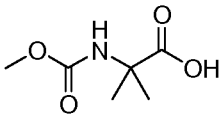
[00185] Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ=2.5 ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, *J*=7.3, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J*=7.3, 3H).

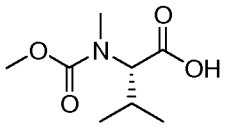
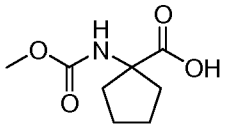
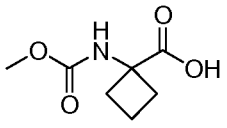
Cap-53 to Cap-64

[00186] Cap-53 to Cap-64 were prepared from appropriate starting materials according to the procedure described for the synthesis of Cap-51, with noted modifications if any.

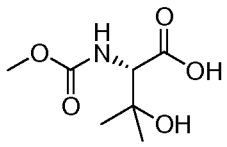
Cap	Structure	Data
Cap-53a: (R) Cap-53b: (S) ((S)-2-(methoxy-carbonyl-amino)butanoic acid)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, *J* = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, *J* = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; found 184.07. HRMS Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; found 184.0592.

Cap	Structure	Data
Cap-54a: (R) Cap-54b: (S) ((S)-2-cyclopropyl-2-(methoxy-carbonyl-amino)acetic acid)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, *J* = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS Calcd. for $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; found 174.0771
Cap-55		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, *J* = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, *J* = 17.1, 1H), 5.04 (d, *J* = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H).
Cap-56 (S)-3-methoxy-2-(methoxy-carbonyl-amino)propanoic acid		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, *J* = 8.3, 0.9H), 6.96 (app s, 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).
Cap-57		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9, 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, *J* = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC-MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.09; found 176.06.

Cap	Structure	Data
Cap-58		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (br s, 1H), 7.35 (s,1H), 7.31 (d, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; found 191.14.
Cap-59a: (R) Cap-59b: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.49 (br s, 1H), 7.40 (d, *J* = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, *J* = 7.3, 3H), 1.15 (t, *J* = 7.2, 3H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.38 (br s, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (two s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; found 160.0604.
Cap-61		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.27 (br s, 1H), 7.40 (br s, 1H), 3.50 (s, 3H), 1.32 (s, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0765.

Cap	Structure	Data
Cap-62		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.74 (br s, 1H), 4.21 (d, *J* = 10.3, 0.6H), 4.05 (d, *J* = 10.0, 0.4H), 3.62/3.60 (two singlets, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). LC-MS: Anal. Calcd. for $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; found 188.05.
Cap-63		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21 (br s, 1H), 7.42 (br s, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; found 188.19.
Cap-64		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (overlapping br s, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

Cap-65

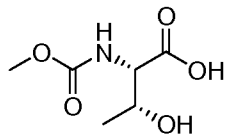


[00187] Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-2-amino-3-hydroxy-3-methylbutanoic acid (1.04 g, 7.81

mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with CH_2Cl_2, and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed *in vacuo* and the residue was taken up in a 2:1 mixture of MeOH/CH_2Cl_2 (15 mL) and filtered, and the filterate was rotervaped to afford Cap-65 as a white semi-viscous foam (1.236 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 6.94 (d, *J* = 8.5, 0.9 H), 6.53 (br s, 0.1H), 3.89 (d, *J* = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

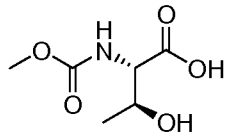
[00188] Cap-66 and Cap-67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of Cap-65.

Cap-66



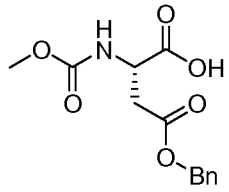
[00189] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



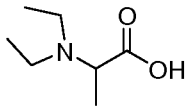
[00190] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted].

Cap-68



[00191] Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and dioxane (9 ml). The reaction mixture was stirred at ambient conditions for 3 hr, and then washed with ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford Cap-68 as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* =16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

Cap-69a and Cap-69b



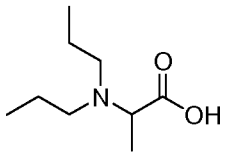
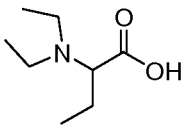
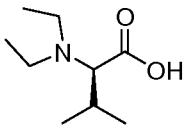
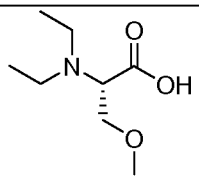
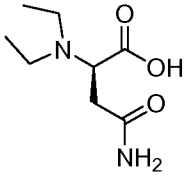
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

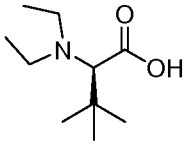
[00192] $NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a DOWEX® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford Cap-69 (2.0 g) as an off-white soft hygroscopic solid. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ

3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

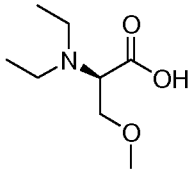
Cap-70 to Cap-74x

[00193] Cap-70 to Cap-74x were prepared according to the procedure described for the synthesis of Cap-69 by employing appropriate starting materials.

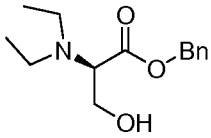
Cap-70a: (R) Cap-70b: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) Cap-71b: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = 7.2, 6H).
Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.

Cap-74x		LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, Step a



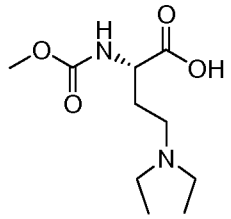
[00194] $NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC ($MeOH/H_2O$/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). LC-MS (Cond. 2): RT = 1.38 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

[00195] NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 µL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the

bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3/Methanol. Removal of the volatile component *in vacuo* afforded Cap-75, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

Cap-76

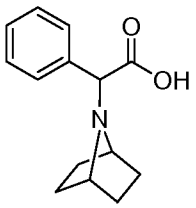


[00196] $NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(*tert*-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with DOWEX® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute NH_4OH, prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

[00197] Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H_2O, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and

washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M NH_3/MeOH) to afford impure Cap-76 as an off-white solid (704 mg). ^{1}H NMR (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, *J* = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, *J* = 7.3, 6H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

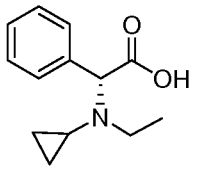
Cap-77a and Cap-77b



Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

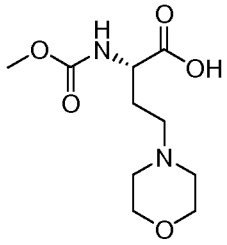
[00198] The synthesis of Cap-77 was conducted according to the procedure described for Cap-7 by using 7-azabicyclo[2.2.1]heptane for the SN_2 displacement step, and by effecting the stereoisomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 um) eluting with 90% CO_2-10% EtOH at 70 mL/min, and a temperature of 35 °C to provide 124.5 mg of stereoisomer-1 and 133.8 mg of stereoisomer-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to provide Cap-77: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; found 232.1340.

Cap-78



[00199] $NaCNBH_3$ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of Cap-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40 mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and $NaCNBH_3$ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotervaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Cap-78 as a colorless viscous oil (353 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz; after D_2O exchange): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, J = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT = 0.64 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; found 220.21. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; found 220.1343.

Cap-79



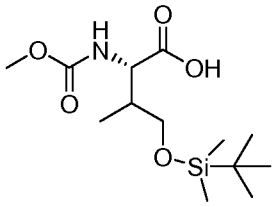
[00200] Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution Cap-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipette drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an

additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

[00201] $NaBH_3CN$ (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of the above crude material and morpholine (500 μL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The volatile component was removed *in vacuo*, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) and a reverse phase HPLC (H_2O/MeOH/TFA) to afford Cap-79 containing unknown amount of morpholine.

[00202] In order to consume the morpholine contaminant, the above material was dissolved in CH_2Cl_2 (1.5 mL) and treated with Et_3N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and H_2O (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed *in vacuo*, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) to afford impure Cap-79 as a brown viscous oil, which was used for the next step without further purification.

Cap-80a and Cap-80b



Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

[00203] $SOCl_2$ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, J = 6.6, 1H), 3.55

(s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

[00204] $Pb(NO_3)_2$ (6.06 g, 18.3 mmol) was added over 1 min to a CH_2Cl_2 (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-phenyl-9*H*-fluorene (6.44 g, 20.0 mmol) and Et_3N (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with $MgSO_4$ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a BIOTAGE® purification (350 g silica gel, CH_2Cl_2 elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J = 12.4, 1H), 4.51 (d, J = 12.6, 1H), 3.78 (d, J = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT = 2.16 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; found 478.19.

[00205] LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for ~1 hr. MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated NH_4Cl solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (100 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was purified with a BIOTAGE® (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio (^1H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^1H NMR data (DMSO-d_6, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, J = 12.3, 1H of CH_2), 3.33 (s, 3H, overlapped with H_2O signal), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); minor diastereomer, δ 4.27 (d, J =12.3, 1H of CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; found 492.15.

[00206] Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (120 mL) solution of (2S)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37 g, 6.86 mmol) prepared above, and stirred at -78 °C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into ~1M H_3PO_4/H_2O (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same column chromatography purification conditions to afford 750 mg of purified material as a white foam. [Note: the (2S, 3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S, 3S) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, *J* = 12.3, 1H), 4.43 (d, *J* = 12.4, 1H), 4.21 (app t, *J* = 5.2, OH), 3.22 (d, *J* = 10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, *J* = 6.8, 3H). LC (Cond. 1): RT = 2.00 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.22. (2S, 3R) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (d, *J* = 7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, *J*= 12.1, 1H), 4.50 (app t, *J* = 4.9, 1H), 4.32 (d, *J* = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, *J* = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, *J* = 6.8, 3H). LC (Cond. 1): RT = 1.92 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.52.

[00207] The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 µL of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (62.7 mg, 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 mL), water (20 mL) and saturated aqueous NH_4Cl solution (1 mL). The organic layer was dried

($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was submitted to a BIOTAGE® purification (40 g silica gel; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate was elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one. (3S,4S)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.83 (d, *J* = 7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, *J* = 8.3, 1H), 3.60 (d, *J* = 5.8, NH), 3.45 (app t, *J* = 9.2, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, *J* = 6.6, 3H). LC (Cond. 1): RT = 1.98 min; LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.89 (d, *J* = 7.6, 1H), 7.85 (d, *J* = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, *J* = 9.1, 4.8, 1H), 3.76 (d, *J* = 8.8, 1H), 2.96 (d, *J* = 3.0, NH), 2.92 (dd, *J* = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, *J* = 7.0, 3H). LC (Cond. 1): RT = 2.03 min; LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.49.

[00208] TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified with a BIOTAGE® (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate. (2S,3S)-silyl ether isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 4.1, 1H), 7.80 (d, *J* = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, *J* = 12.4, 1H), 4.42 (d, *J* = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, *J* = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, *J* = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT = 3.26 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: ^{1}H

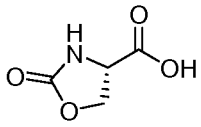
NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 3.0, 1H), 7.80 (d, *J* = 3.1, 1H), 7.39-7.10 (m, 16H), 4.66 (d, *J* = 12.4, 1H), 4.39 (d, *J* = 12.4, 1H), 3.61 (dd, *J* = 9.9, 5.6, 1H), 3.45 (d, *J* = 9.5, 1H), 3.41 (dd, *J* = 10, 6.2, 1H), 2.55 (dd, *J* = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, *J* = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

[00209] A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged with H_2 as necessary. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of diatomaceous earth (CELITE®-545), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/H_2O) to afford (2S,3S)-2-amino-4-(*tert*-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(*tert*-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: ^{1}H NMR (methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76 (dd, *J* = 10.5, 5.2, 1H), 3.73 (d, *J* = 3.0, 1H), 3.67 (dd, *J* = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, *J* = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: ^{1}H NMR (methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, *J* = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, *J* = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

[00210] Water (1 mL) and NaOH (0.18 mL of 1.0 M/H_2O, 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(*tert*-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and Na_2CO_3 (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with CH_2Cl_2 (15 mL, 2x). The combined

organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford Cap-80a as an off-white solid. (2S,3R)-2-amino-4-(*tert*-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to Cap-80b. Cap-80a: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, J = 8.3, 0.3H), 7.19 (d, J = 8.8, 0.7H), 4.44 (dd, J = 8.1, 4.6, 0.3H), 4.23 (dd, J = 8.7, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with *t*-Bu signal), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (three overlapping singlets, 6H). LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. Cap-80b: ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz), 6.00 (br d, J = 6.8, 1H), 4.36 (dd, J = 7.1, 3.1, 1H), 3.87 (dd, J = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, J = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, J = 7.1, 3H), 0.90 (s, 9H), 0.08 (s, 6H). LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

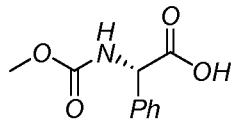
Cap-81



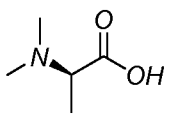
[00211] Prepared according to the protocol described by Falb et al., *Synthetic Communications*, 23:2839 (1993).

Cap-82 to Cap-85

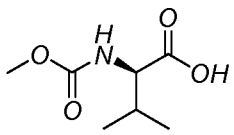
[00212] Cap-82 to Cap-85 were synthesized from appropriate starting materials according to the procedure described for Cap-51 or Cap-13. The samples exhibited similar spectral profiles as that of their stereoisomers (*i.e.*, Cap-4, Cap-13, Cap-51 and Cap-52, respectively).



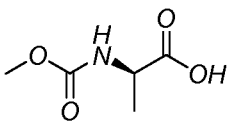
Cap-82



Cap-83

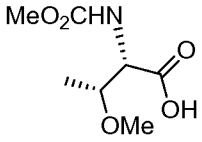


Cap-84



Cap-85

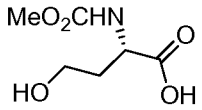
Cap-86



(2S,3R)-3-Methoxy-2-(methoxycarbonylamino)butanoic acid

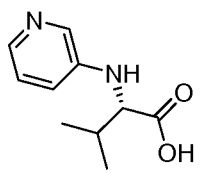
[00213] To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0 °C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, J = 7.7 Hz, 3H). LC-MS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 $(M-H)^-$.

Cap-87



[00214] To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0 °C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 - 2.14 (m, 1H), 1.82 - 1.89 (m, 1H). LC-MS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

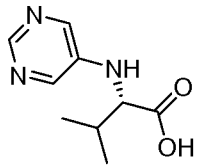
Cap-88



[00215] A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL)

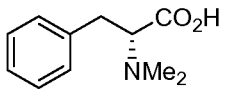
was heated at 100 °C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, br, 1H), 7.68 - 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 - 2.06 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). LC-MS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

Cap-89



[00216] A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100 °C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}H NMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity could not be estimated. The material was used as is in subsequent reactions. LC-MS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

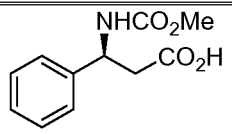
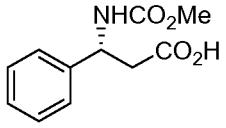
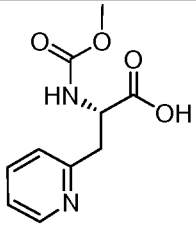
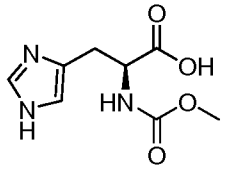
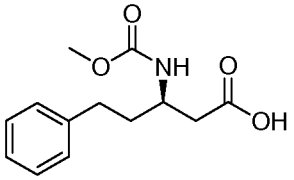
Cap-90

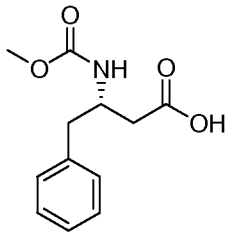
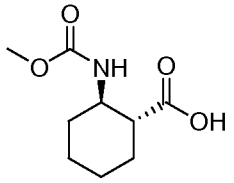
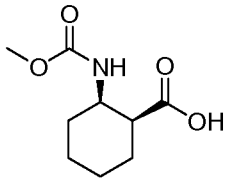
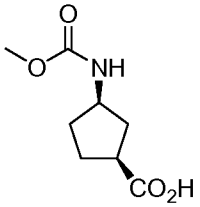
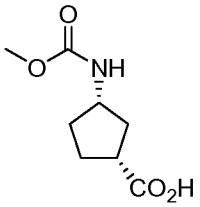
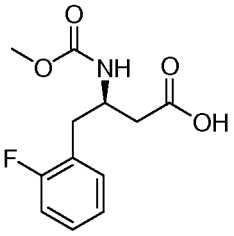


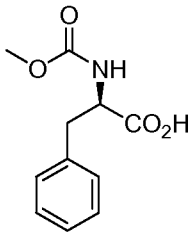
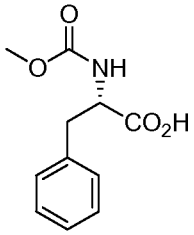
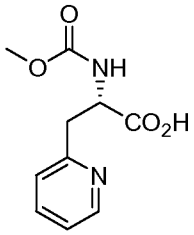
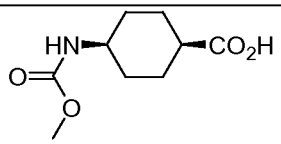
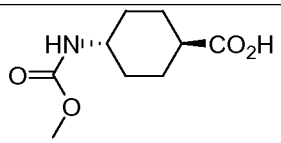
[00217] Cap-90 was prepared according to the method described for the preparation of Cap-1. The crude material was used as is in subsequent steps. LC-MS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

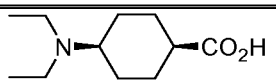
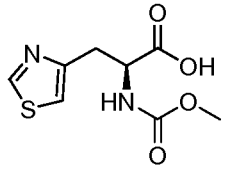
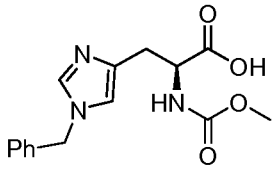
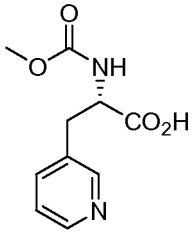
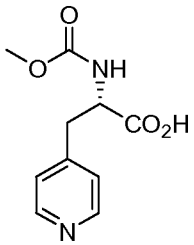
Cap-91 to Cap-116

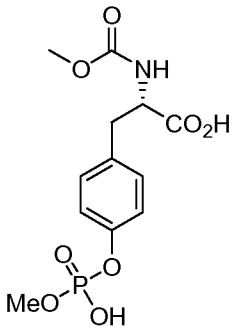
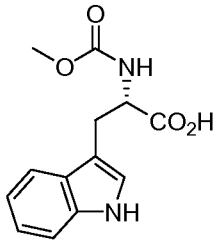
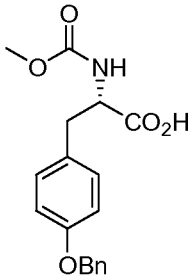
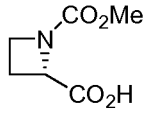
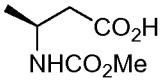
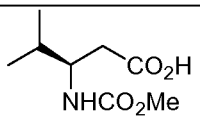
[00218] The following Caps were prepared according to the method used for preparation of Cap-51 unless noted otherwise:

Cap	Structure	LC-MS
Cap-91		LC-MS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-92		LC-MS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-93		LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-94		LC-MS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.
Cap-95		LC-MS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 $(M-H)^-$.

Cap	Structure	LC-MS
Cap-96		LC-MS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 $(M-H)^-$.
Cap-97		LC-MS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 $(M-H)^-$.
Cap-98		LC-MS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$.
Cap-99		^{1}H NMR (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 - 1.94 (m, 3H), 1.45 - 1.71 (m, 2H).
Cap-99a		^{1}H NMR (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 - 1.94 (m, 3H), 1.45 - 1.71 (m, 2H).
Cap-100		LC-MS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$.

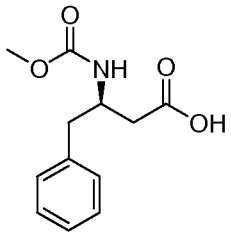
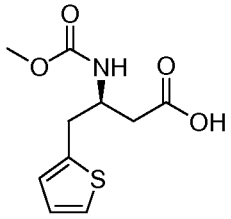
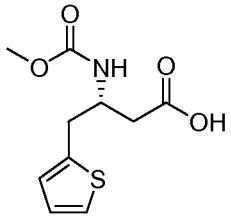
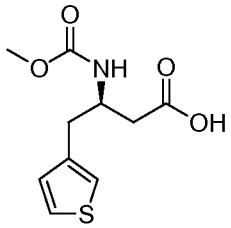
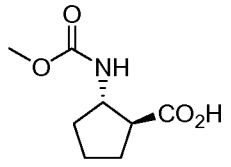
Cap	Structure	LC-MS
Cap-101		LC-MS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LC-MS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}H NMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 - 3.53 (m, 1H), 2.66 - 2.69 and 2.44 - 2.49 (m, 1H), 1.91 - 2.01 (m, 2H), 1.62 - 1.74 (m, 4H), 1.51 - 1.62 (m, 2H).
Cap-105		^{1}H NMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 - 3.35 (m, 1H, partially obscured by solvent), 2.37 - 2.41 and 2.16 - 2.23 (m, 1H), 1.94 - 2.01 (m, 4H), 1.43 - 1.53 (m, 2H), 1.17 - 1.29 (m, 2H).

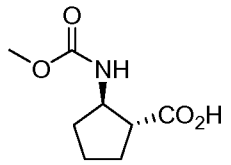
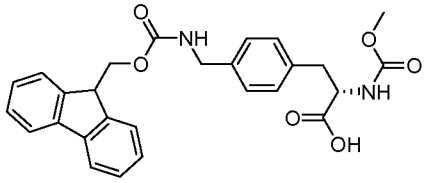
Cap	Structure	LC-MS
Cap-106	 Prepared from cis-4-aminocyclohexane carboxylic acid and acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N NH_3/MeOH elution) to afford an oil, which was dissolved in CH_3CN/H_2O and lyophilized to afford a tan solid.	^{1}H NMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 - 2.31 (m, 2H), 1.79 - 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H)
Cap-107		LC-MS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LC-MS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LC-MS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.

Cap	Structure	LC-MS
Cap-111		LC-MS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LC-MS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.
Cap-113		LC-MS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 - 4.84 (m, 1H), 4.00 - 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Cap-115		^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, *J* = 5.0 Hz, 2H), 1.28 (d, *J* = 9.1 Hz, 3H).
Cap-116		^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 8.6 Hz, 1H), 3.74 - 3.83 (m, 1H), 3.69 (s, 3H), 2.54 - 2.61 (m, 2H), 1.88 (sept, *J* = 7.0 Hz, 1H), 0.95 (d, *J* = 7.0 Hz, 6H).

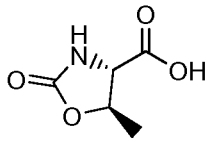
Cap-117 to Cap-123

[00219] For the preparation of Cap-117 to Cap-123 the Boc amino acids were obtained from commercially sources and were deprotected by treatment with 25% TFA in CH_2Cl_2. After complete reaction as judged by LC-MS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure described for Cap-51.

Cap	Structure	LC-MS
Cap-117		LC-MS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 238 $(M+H)^+$.
Cap-118		LC-MS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-119		LC-MS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-120		LC-MS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-121		^1H NMR (400 MHz, $CDCl_3$) δ 4.06 - 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 - 2.10 (m, 3H), 1.64 - 1.76 (m, 2H), 1.44 - 1.53 (m, 1H).

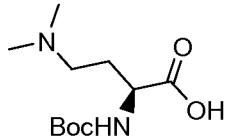
Cap	Structure	LC-MS
Cap-122		^{1}H NMR profile is similar to that of its stereoisomer, Cap-121.
Cap-123		LC-MS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

Cap-124



[00220] The hydrochloride salt of L-threonine *tert*-butyl ester was carbamoylated according to the procedure for Cap-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless oil which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-CH_2Cl_2-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless oil which was shown by LC-MS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LC-MS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

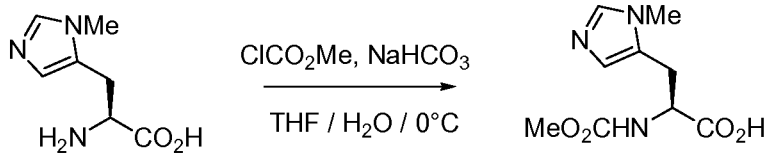
Cap-125



[00221] To a suspension of $Pd(OH)_2$, (20%, 100 mg), aqueous formaldehyde (37% wt, 4 ml), acetic acid, (0.5 mL) in methanol (15 mL) was added (S)-4-amino-2-(*tert*-butoxycarbonylamino)butanoic acid (1 g, 4.48 mmol). The reaction was purged several

times with hydrogen and was stirred overnight with an hydrogen balloon room temperature. The reaction mixture was filtered through a pad of diatomaceous earth (CELITE®), and the volatile component was removed *in vacuo*. The resulting crude material was used as is for the next step. LC-MS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Cap-126

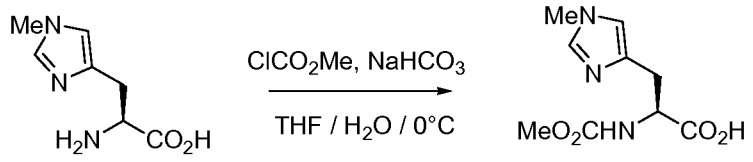


cj-25 *cap-126*

[00222] This procedure is a modification of that used to prepare Cap-51. To a suspension of 3-methyl-L-histidine (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0 °C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0 °C. After stirring for ca. 2h LC-MS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

[00223] The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LC-MS and ^1H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and H_2O (10mL), cooled to 0 °C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LC-MS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LC-MS and ^1H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification. ^1H NMR (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, J = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, J = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd, J = 9.0, 15.6 Hz, 1H).LC-MS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228.09 $(M+H)^+$.

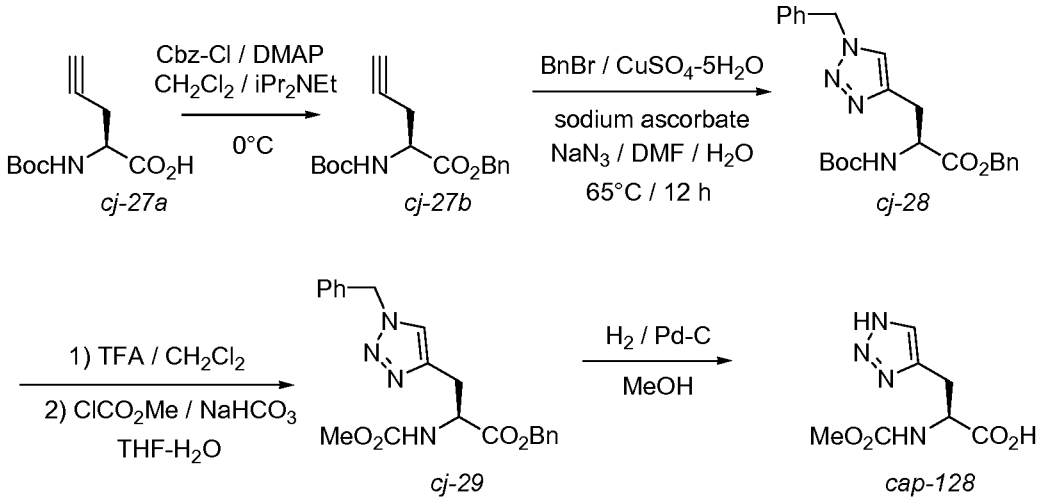
Cap-127



cj-26 *cap-127*

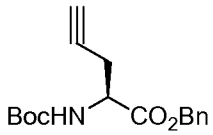
[00224] Cap-127 was prepared according to the method for Cap-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LC-MS and ^1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification. ^1H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, J = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H); LC-MS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228 $(M+H)^+$.

Preparation of Cap-128



cj-27a *cj-27b* *cj-28* *cj-29* *cap-128*

Step 1. Preparation of (S)-benzyl 2-(*tert*-butoxycarbonylamino)pent-4-ynoate (cj-27b).

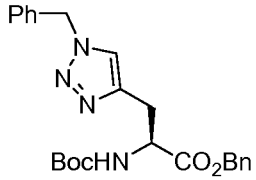


cj-27b

[00225] To a solution of cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr_2NEt (1.7 mL, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added Cbz-Cl (0.68 mL,

4.83 mmol). The solution was allowed to stir for 4 h at 0 °C, washed (1N $KHSO_4$, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d, br, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48 - 4.53 (m, 1H), 2.68 - 2.81 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.44 (s, 9H). LC-MS: Anal. Calcd. for $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

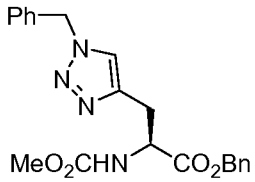
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(*tert*-butoxycarbonylamino)propanoate (cj-28).



cj-28

[00226] To a mixture of (S)-benzyl 2-(*tert*-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in DMF-H_2O (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65 °C. After 5h LC-MS indicated low conversion. A further portion of NaN_3 (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H_2O x3, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (BIOTAGE®, 40+M 0-5% MeOH in CH_2Cl_2; TLC 3% MeOH in CH_2Cl_2) to afford a light yellow oil which solidified on standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27 - 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, J = 1.0, 5.3 Hz, 1H), 3.06 (dd, J = 5.3, 14.7 Hz), 2.96 (dd, J = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H). LC-MS: Anal. Calcd. for $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

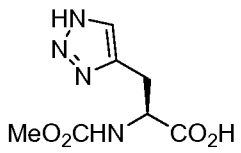
Step 3. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



cj-29

[00227] A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(*tert*-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH_2Cl_2 was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This material was dissolved in THF-H_2O and cooled to 0 °C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into H_2O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27 - 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32 - 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). LC-MS: Anal. Calcd. for $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

Step 4. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (Cap-128).

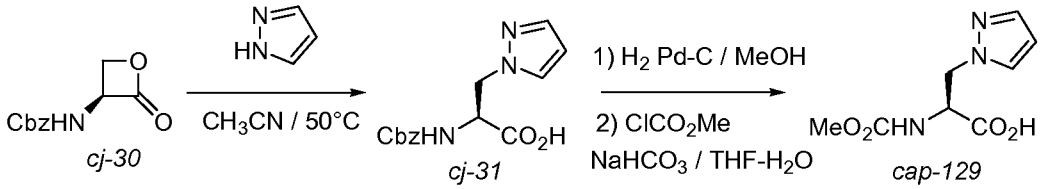


Cap-128

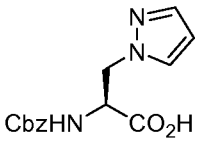
[00228] (S)-Benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture

was filtered through diatomaceous earth (CELITE®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 4.19 - 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, *J* = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, *J* = 9.9, 15.0 Hz, 1H). LC-MS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of Cap-129



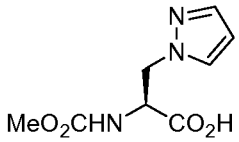
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



cj-31

[00229] A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH_3CN (12 mL) was heated at 50 °C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of CH_3CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%). m.p. 165.5 - 168 °C. lit m.p. 168.5 - 169.5 [Vederas et al., *J. Am. Chem. Soc.*, 107:7105 (1985)]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 2.0, 1H), 7.48 (s, *J* = 1.5 Hz, 1H), 7.24 - 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 4.59 - 4.66 (m, 2H), 4.42 - 4.49 (m, 1H). LC-MS: Anal. Calcd. for $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

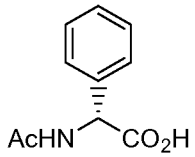
Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (Cap-129).



cap-129

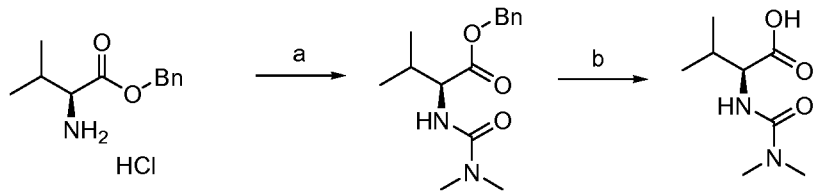
[00230] (S)-2-(Benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the reaction mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (CELITE®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-H_2O (1:1, 10mL) and then cooled to 0 °C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of CO_2). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extracted with EtOAC (x5). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.19 (app t, J = 2.0 Hz, 1H), 4.47 (dd, J = 3.0, 12.9 Hz, 1H), 4.29 - 4.41 (m, 2H), 3.48 (s, 3H). LC-MS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

Cap-130



[00231] Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analogous to the procedure given in: Calmes, M. et al., *Tetrahedron*, 43(10):2285 (1987).

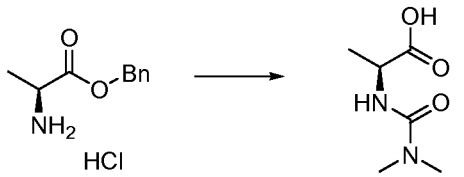
Cap-131



[00232] Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of clear oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). LC (Cond. 1): RT = 1.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; found 279.03.

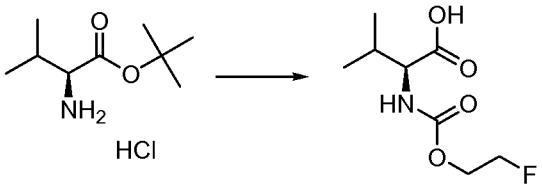
[00233] Step b: To an MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of Cap-131 as a white foam, which was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). LC (Cond. 1): RT = 0.33 min; MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.04.

Cap-132



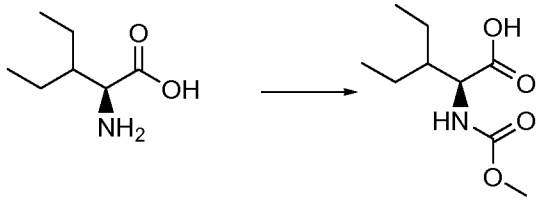
[00234] Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for Cap-131. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.

Cap-133



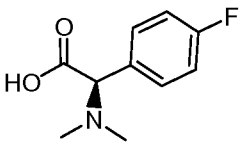
[00235] Cap-133 was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for Cap-47. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, *J* = 8.54 Hz, 1H), 12.54 (s, 1H).

Cap-134



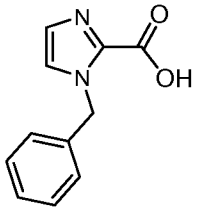
[00236] Cap-134 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for Cap-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; found 204.02.

Cap-135



[00237] A solution of D-2-amino-(4-fluorophenyl)acetic acid (338 mg, 2.00 mmol), 1*N* HCl in diethylether (2.0 mL, 2.0 mmol) and formalin (37%, 1 mL) in methanol (5 mL) was subjected to balloon hydrogenation over 10% palladium on carbon (60 mg) for 16 h at 25 °C. The mixture was then filtered through CELITE® to afford the HCl salt of Cap-135 as a white foam (316 mg, 80%). ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.59 (dd, J = 8.80, 5.10 Hz, 2H), 7.29 (t, J = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (v br s, 3H), 2.63 (v br s, 3H); R_t = 0.19 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

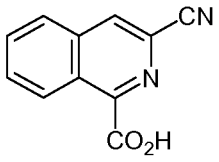
Cap-136



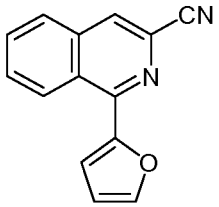
[00238] To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was bubbled into the reaction mixture for 10 min before it was allowed to warm up to 25 °C. The heavy precipitate which formed on addition of carbon dioxide to the reaction mixture was filtered to yield a hygroscopic, white solid which was taken up in water (7 mL), acidified to pH = 3, cooled, and induced to crystallize with scratching. Filtration of this precipitate gave a white solid which was suspended in methanol, treated with 1*N* HCl/diethyl ether (4 mL) and concentrated *in vacuo*. Lyophilization of the residue from water (5 mL) afforded the HCl salt of Cap-136 as a white solid (817 mg, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.50-7.31 (m, 5H), 5.77 (s, 2H); R_t = 0.51 min (Cond.-MS-

W5); 95% homogenity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; found: 203.11.

Cap-137

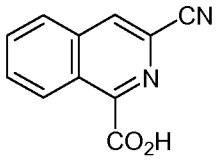


Cap-137, Step a



[00239] A suspension of 1-chloro-3-cyanoisoquinoline (188 mg, 1.00 mmol; prepared according to the procedure in WO 2003/099274) (188 mg, 1.00 mmol), cesium fluoride (303.8 mg, 2.00 mmol), bis(tri-*tert*-butylphosphine)palladium dichloride (10 mg, 0.02 mmol) and 2-(tributylstannyl)furan (378 μL, 1.20 mmol) in anhydrous dioxane (10 mL) under nitrogen was heated at 80 °C for 16 h before it was cooled to 25 °C and treated with saturated, aqueous potassium fluoride solution with vigorous stirring for 1 h. The mixture was partitioned between ethyl acetate and water and the organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification of the residue on silica gel (elution with 0% to 30% ethyl acetate/hexanes) afforded Cap-137, Step a as a white solid which was used as is (230 mg, 105%). R_t = 1.95 min (Cond.-MS-W2); 90% homogeneity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; found: 221.12.

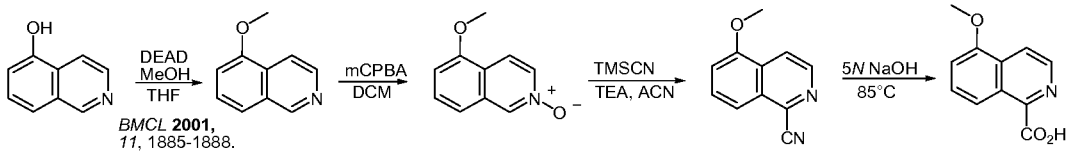
Cap-137



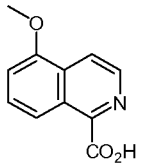
[00240] To a suspension of Cap-137, Step a (110 mg, 0.50 mmol) and sodium periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL) and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol). The mixture was stirred at 25 °C for 2 h and then partitioned between dichloromethane and water. The aqueous layer was separated, extracted twice more with dichloromethane and the combined dichloromethane extracts were dried over Na_2SO_4, filtered and concentrated. Trituration of the residue with hexanes afforded Cap-137 (55 mg, 55%) as a grayish-colored solid. R_t = 1.10 min (Cond.-MS-W2); 90% homogeneity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; found: 200.08.

Cap-138 to Cap-158

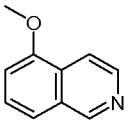
Synthetic Strategy. Method A.



Cap-138



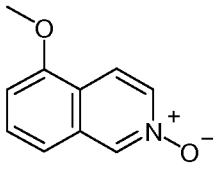
Cap-138, Step a



[00241] To a stirred suspension of 5-hydroxisoquinoline (prepared according to the procedure in WO 2003/099274) (2.0 g, 13.8 mmol) and triphenylphosphine (4.3 g, 16.5 mmol) in dry tetrahydrofuran (20 mL) was added dry methanol (0.8 mL) and diethyl azodicarboxylate (3.0 mL, 16.5 mmol) portionwise. The mixture was stirred at room temperature for 20 h before it was diluted with ethyl acetate and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was preabsorbed onto silica gel and

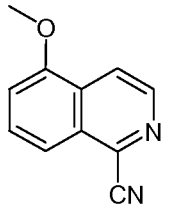
purified (elution with 40% ethyl acetate/hexanes) to afford Cap-138, Step a as a light yellow solid (1.00 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); R_t = 0.66 min (Cond. D2); 95% homogeneity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; found 160.10.

Cap-138, Step b



[00242] To a stirred solution of Cap-138, Step a (2.34 g, 14.7 mmol) in anhydrous dichloromethane (50 mL) at room temperature was added *meta*-chloroperbenzoic acid (77%, 3.42 g, 19.8 mmol) in one portion. After being stirred for 20 h, powdered potassium carbonate (2.0 g) was added and the mixture was stirred for 1 h at room temperature before it was filtered and concentrated to afford Cap-138, Step b as a pale, yellow solid which was sufficiently pure to carry forward (2.15 g, 83.3%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 7.3, 1.7 Hz, 1H), 8.04 (d, J=7.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.00 (s, 3H); R_t = 0.92 min, (Cond.-D1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; found: 176.0.

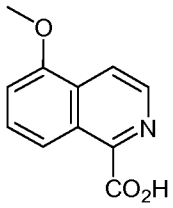
Cap-138, Step c



[00243] To a stirred solution of Cap-138, Step b (0.70 g, 4.00 mmol) and triethylamine (1.1 mL, 8.00 mmol) in dry acetonitrile (20 mL) at room temperature under nitrogen was added trimethylsilylcyanide (1.60 mL, 12.00 mmol). The mixture was heated at 75 °C for 20 h before it was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine prior to drying over Na_2SO_4 and solvent

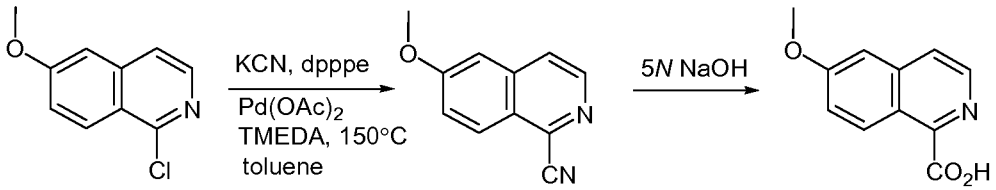
concentration. The residue was flash chromatographed on silica gel (elution with 5% ethyl acetate/hexanes) to 25% ethyl acetate/hexanes to afford Cap-138, Step c (498.7 mg) as a white, crystalline solid along with 223 mg of additional Cap-138, Step c recovered from the filtrate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 4.04 (s, 3H); R_t = 1.75 min, (Cond.-D1); 90% homogeneity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.10.

Cap-138



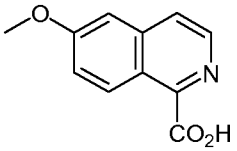
[00244] Cap-138, Step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over Na_2SO_4, concentrated to ¼ volume and filtered to afford Cap-138 as a yellow solid (0.44g, 88.9%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.6 (br s, 1H), 8.56 (d, J = 6.0 Hz, 1H), 8.16 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H); R_t = 0.70 min (Cond.-D1); 95% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Synthetic Strategy. Method B (derived from *Tetrahedron Letters*, 42:6707 (2001)).

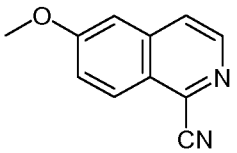


WO 2003/ 099274

Cap-139

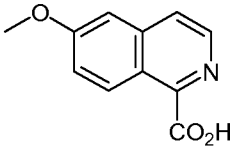


Cap-139, Step a



[00245] To a thick-walled, screw-top vial containing an argon-degassed suspension of 1-chloro-6-methoxyisoquinoline (1.2 g, 6.2 mmol; prepared according to the procedure in WO 2003/099274), potassium cyanide (0.40 g, 6.2 mmol), 1,5-bis(diphenylphosphino)pentane (0.27 g, 0.62 mmol) and palladium (II) acetate (70 mg, 0.31 mmol) in anhydrous toluene (6 mL) was added *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (0.29 mL, 2.48 mmol). The vial was sealed, heated at 150 °C for 22 h and then allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 5% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to afford Cap-139, Step a as a white solid (669.7 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.54 (d, J = 6.0 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H); R_t = 1.66 min (Cond.-D1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.20.

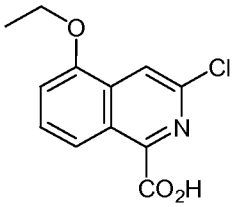
Cap-139



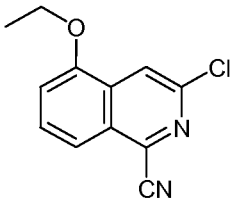
[00246] Cap-139 was prepared from the basic hydrolysis of Cap-139, Step a with 5*N* NaOH according to the procedure described for Cap-138. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (v br s, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); R_t = 0.64

min (Cond.-D1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Cap-140

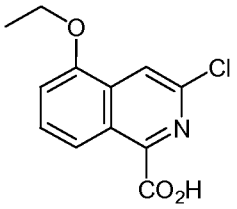


Cap-140, Step a



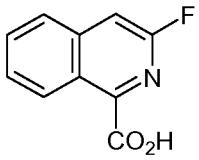
[00247] To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (2 mL) at 25 °C under nitrogen was added N,N,N′,N′-tetramethylethylenediamine (60 mL, 0.40 mmol). After 10 min, the mixture was heated to 150 °C, and then a stock solution of acetone cyanohydrin (prepared from 457 μL of acetone cyanohydrin in 4.34 mL DMA) was added in 1 mL portions over 18 h using a syringe pump. The mixture was then partitioned between ethyl acetate and water and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel eluting with 10% ethyl acetate/hexanes to 40% ethyl acetate/hexanes to afford Cap-140, Step a as a yellow solid (160 mg, 34%). R_t = 2.46 min (Cond.-MS-W2); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; found: 233.08.

Cap-140

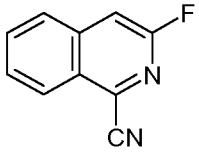


[00248] Cap-140 was prepared by the acid hydrolysis of Cap-140, Step a with 12*N* HCl as described in the procedure for the preparation of Cap-141, described below. R_t = 2.24 min (Cond.-MS-W2); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

Cap-141

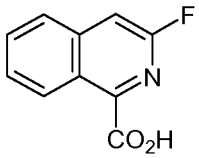


Cap-141, Step a



[00249] Cap-141, Step a was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.*, 13:613 (1970)) as described in the procedure for the preparation of Cap-140, Step a (*vide supra*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); R_t = 1.60 min (Cond.-D1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; found: 172.99.

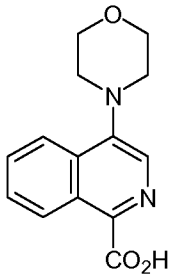
Cap-141



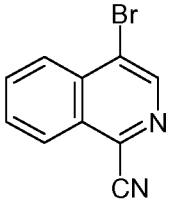
[00250] Cap-141, Step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature

and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford Cap-141 as an off-white solid (44.1 mg, 47.8%). The filtrate was diluted with dichloromethane and washed with brine, dried over Na_2SO_4, and concentrated to afford additional Cap-141 which was sufficiently pure to be carried forward directly (29.30 mg, 31.8%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 14.0 (br s, 1H), 8.59-8.57 (m, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); R_t = 1.33 min (Cond.-D1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 191.97.

Cap-142

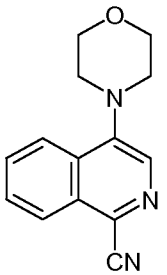


Cap-142, Step a



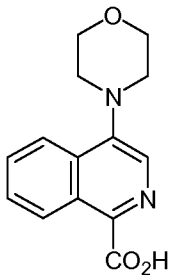
[00251] Cap-142, Step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of Cap-138, steps b and c. R_t = 1.45 min (Cond.-MS-W1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

Cap-142, Step b



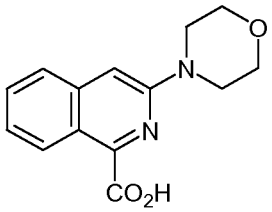
[00252] To an argon-degassed suspension of Cap-142, Step a (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 μL, 0.70 mmol). The mixture was heated at 100 °C for 16 h, cooled to 25 °C and filtered through diatomaceous earth (CELITE®). Purification of the residue on silica gel, eluting with 10% to 70% ethyl acetate/hexanes afforded Cap-142, Step b (38 mg, 32%) as a yellow solid, which was carried forward directly. R_t = 1.26 min (Cond.-MS-W1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; found: 240.13.

Cap-142

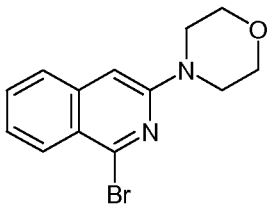


[00253] Cap-142 was prepared from Cap-142, Step b with 5*N* sodium hydroxide as described in the procedure for Cap-138. R_t = 0.72 min (Cond.-MS-W1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-143

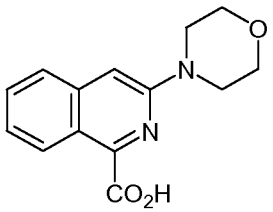


Cap-143, Step a



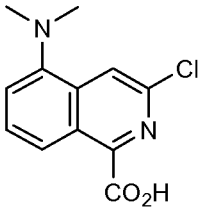
[00254] To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 μL, 2.00 mmol) was added. The mixture was stirred further at 25 °C for 5 h and at 75 °C for 72 h before it was cooled to 25 °C, quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. Purification of the residue on silica gel eluting with 0% to 70% ethyl acetate/hexanes afforded Cap-143, Step a as a yellow solid (180 mg, 31%). R_t = 1.75 min (Cond.-MS-W1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; found: 293.04.

Cap-143

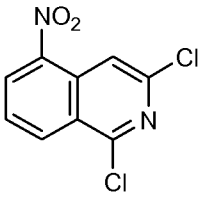


[00255] To a cold (-60 °C) solution of Cap-143, Step a (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into the reaction mixture for 10 min before it was quenched with 1*N* HCl and allowed to warm to 25 °C. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were concentrated *in vacuo*. Purification of the residue by a reverse phase HPLC (MeOH/water/TFA) afforded Cap-143 (16 mg, 12%). R_t = 1.10 min (Cond.-MS-W1); 90% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-144

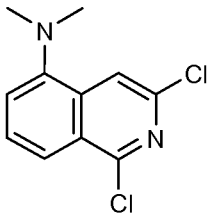


Cap-144, Step a



[00256] 1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured into a beaker containing chopped ice and water and the resulting suspension was stirred for 1 h at 0 °C before it was filtered to afford Cap-144, Step a (2.73 g, 81%) as a yellow solid which was used directly. R_t = 2.01 min. (Cond.-D1); 95% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; found: 242.92.

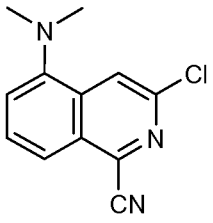
Cap-144, Step b



[00257] Cap-144, Step a (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi H_2 for 1.5 h. Then formalin (5 mL) and additional platinum oxide (30 mg) were added, and the suspension was resubjected to Parr hydrogenation at 45 psi H_2 for 13 h. It was then suction-filtered through diatomaceous earth (CELITE®) and concentrated down to ¼ volume. Suction-filtration of the ensuing precipitate afforded the

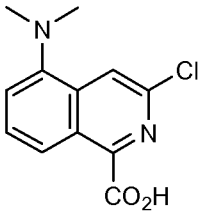
title compound as a yellow solid which was flash chromatographed on silica gel eluting with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes to afford Cap-144, Step b (231 mg, 78%) as a pale yellow solid. R_t = 2.36 min (Cond.-D1); 95% homogenity index; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, J = 7.3 Hz, 1H), 2.88 (s, 6H); LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; found: 241.02. HRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; found: 241.0296.

Cap-144, Step c



[00258] Cap-144, Step c was prepared from Cap-144, Step b according to the procedure described for the preparation of Cap-139, Step a. R_t = 2.19 min (Cond.-D1); 95% homogenity index; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; found: 232.03. HRMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; found: 232.0631.

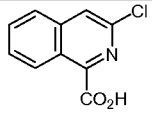
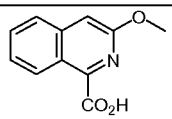
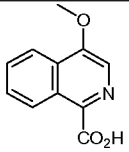
Cap-144

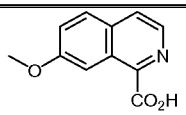
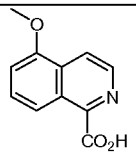
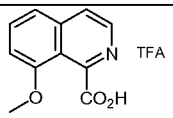


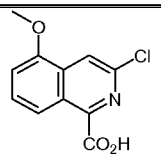
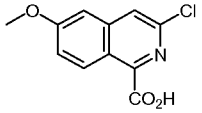
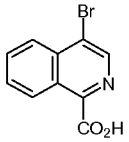
[00259] Cap-144 was prepared according to the procedure described for Cap-141. R_t = 2.36 min (Cond.-D1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

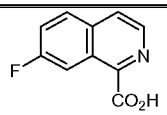
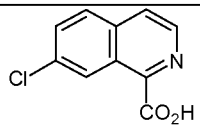
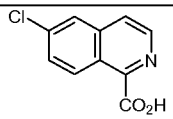
Cap-145 to Cap-162

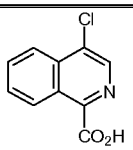
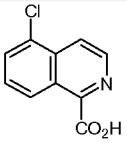
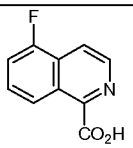
[00260] Cap-145 to Cap-162 were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of Cap-138 (Method A) or Cap-139 (Method B) unless noted otherwise as outlined below.

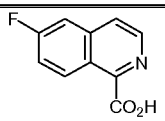
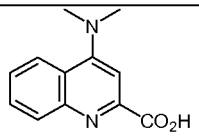
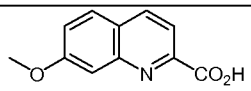
Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-145	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12*N* HCl	1.14 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-146	 Prepared from commercially available 3-hydroxyisoquinoline	A	5*N* NaOH	1.40 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.06.
Cap-147	 Prepared from commercially available 1-chloro-4-hydroxyisoquinoline	B	5*N* NaOH	0.87 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-148	 Prepared from commercially available 7-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-149	 Prepared from commercially available 5-hydroxyisoquinoline	A	5*N* NaOH	0.70 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-150	 Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	A	12*N* HCl	0.26 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.04.

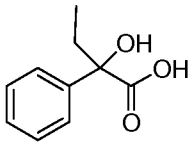
Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-151 3-chloro-5-methoxyisoquinoline-1-carboxylic acid	 Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure in WO 2005/051410	B	12*N* HCl	1.78 min (Cond.-D1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; found: 238.09.
Cap-152	 Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline	B	12*N* HCl	1.65 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; found: 238.09.
Cap-153	 Prepared from 4-bromoisoquinoline, which can be synthesized following the procedure in WO 2003/062241	A	6*N* HCl	1.18 min (Cond.-MS-W1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; found: 251.95.

Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-154	 Prepared from 7-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.28 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-155	 Prepared from 1,7-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.59 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-156	 Prepared from 1,6-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.60 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.03.

Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-157	 Prepared from 1,4-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/062241	B	12*N* HCl	1.49 min (Cond.-D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; found: 208.00.
Cap-158	 Prepared from 1,5-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.69 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.01.
Cap-159	 Prepared from 5-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.41 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.

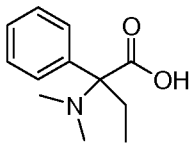
Cap-#	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-160	 Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* NaOH	0.30 min (Cond.-MS-W1); 90%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-161	 Prepared from 4-bromoquinoline-2-carboxylic acid and dimethylamine (DMSO, 100 °C)	--	--	0.70 min (Cond. D1); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; found: 217.06.
Cap-162	 Prepared from m-anisidine following the procedure described in *J. Hetero. Chem.*, 17 (1993) and *Heterocycles*, 60:953 (2003).	--	--	0.65 min (Cond.-M3); 95%; LC-MS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 203.94.

Cap-163



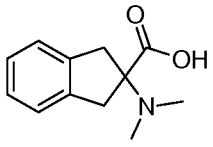
[00261] To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over $MgSO_4$. After concentration *in vacuo*, a white solid was obtained. The solid was recrystallized from hexanes/ethyl acetate to afford Cap-163 as white needles (883.5 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.71 (br s, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (br s, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (app t, J = 7.4 Hz, 3H).

Cap-164



[00262] A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to H_2 at 50 psi in a Parr bottle for 42 h. The reaction was filtered over CELITE® and concentrated *in vacuo*, the residue was taken up in MeOH (36 mL) and the product was purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of Cap-164 as a white solid (1.7 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (app t, J = 7.3 Hz, 3H).

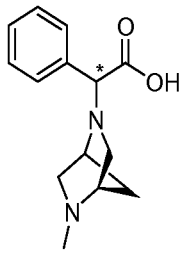
Cap-165



[00263] To a mixture of 2-amino-2-indanecarboxylic acid (258.6 mg, 1.46 mmol) and formic acid (0.6 ml, 15.9 mmol) in 1,2-dichloroethane (7 ml) was added formaldehyde (0.6 ml, 37% in water). The mixture was stirred at ~25 °C for 15 min then heated at 70

°C for 8h. The volatile component was removed *in vacuo*, and the residue was dissolved in DMF (14 mL) and purified by a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of Cap-165 as a viscous oil (120.2 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found: 206.07.

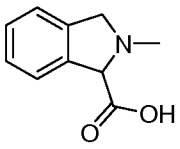
Cap-166a and Cap-166b



Cap-166a: Diastereomer-1
Cap-166b: Diastereomer-2

[00264] Cap-166a and Cap-166b were prepared from (1S, 4S)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2HBr) according to the method described for the synthesis of Cap-7a and Cap-7b, with the exception that the benzyl ester intermediate was separated using a semi-prep Chrialcel OJ column, 20 x 250 mm, 10 μm eluting with 85:15 heptane/ethanol mixture at 10 mL/min elution rate for 25 min. Cap-166b: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (app br s, 1H), 3.16 (app br s, 1H), 2.83 (d, *J*=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 1.77 (d, J = 9.8 Hz, 1H), 1.63 (d, J = 9.8 Hz, 1H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; found: 247.11.

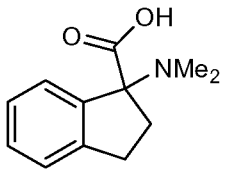
Cap-167



[00265] A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/CH_2Cl_2 was stirred at ~25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in MeOH was exposed to H_2 (40 PSI) in a Parr bottle for 23 h. The reaction mixture was filtered over CELITE® and concentrated *in vacuo* to afford Cap-167 as a yellow foam (873.5 mg). ^{1}H NMR (DMSO-

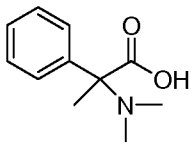
d_6, δ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; found: 178.65.

Cap-168



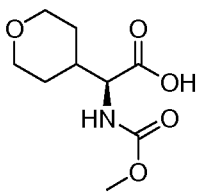
[00266] Racemic Cap-168 was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of Cap-167. The crude material was employed as such.

Cap-169



[00267] A mixture of 2-amino-2-phenylpropanoic acid hydrochloride (5.0 g, 2.5 mmol), formaldehyde (15 ml, 37% in water), 1N HCl (15 ml), and 10% Pd/C (1.32 g) in MeOH (60 mL) was placed in a Parr bottle and shaken under hydrogen (55 PSI) for 4 days. The reaction mixture was filtered over CELITE® and concentrated *in vacuo*. The residue was taken up in MeOH and purified by reverse phase prep-HPLC (MeOH/water/TFA) to afford the TFA salt of Cap-169 as a viscous semi-solid (2.1 g). ^1H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 7.58-7.52 (m, 2 H), 7.39-7.33 (m, 3H), 2.86 (br s, 3H), 2.47 (br s, 3H), 1.93 (s, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found: 194.12.

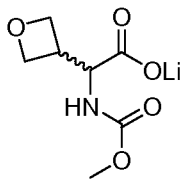
Cap-170



(S)-2-(Methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid

[00268] To (*S*)-2-amino-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (505mg; 3.18mmol; obtained from Astatech) in water (15ml) was added sodium carbonate (673mg; 6.35mmol), and the resultant mixture was cooled to 0 °C and then methyl chloroformate (0.26ml; 3.33mmol) was added dropwise over 5 minutes. The reaction was allowed to stir for 18 hours while allowing the bath to thaw to ambient temperature. The reaction mixture was then partitioned between 1N HCl and ethyl acetate. The organic layer was removed and the aqueous layer was further extracted with 2 additional portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford Cap-170 a colorless residue. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.65 (1 H, br s), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2 H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; found 218.1.

Cap-171

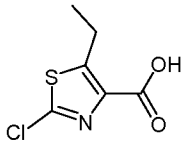


[00269] A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (200 mg, 0.721 mmol; *Il Farmaco*, 56:609-613 (2001)) in ethyl acetate (7 ml) and CH_2Cl_2 (4.00 ml) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 ml, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight at which time TLC (95:5 CH_2Cl_2 / MeOH: visualized with stain made from 1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water) indicated complete conversion. The reaction was filtered through CELITE® and concentrated. The residue was purified via BIOTAGE® (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% MeOH / dichloromethane over 250ml then hold at 5% MeOH / dichloromethane for 250ml; 9ml fractions). Collected fractions containing desired material and concentrated to 120mg

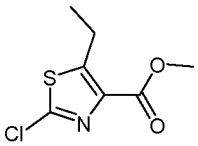
(81%) of methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (br s, 1 H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; found 204.0.

[00270] To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnight at ambient temperature. TLC (1:1 EA / Hex; Hanessian stain [1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water]) indicated ~10% starting material remaining. Added an additional 3mg LiOH and allowed to stir overnight at which time TLC showed no starting material remaining. Concentrated *in vacuo* and placed on high vac overnight providing 55 mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. ^{1}H NMR (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

Cap-172



Cap-172, Step a



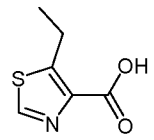
[00271] The following diazotization step was adapted from Barton, A. et al., *J.C.S. Perkin Trans I*, 159-164 (1982): A solution of $NaNO_2$ (166 mg, 2.4 mmol) in water (0.6 mL) was added slowly to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol), $CuSO_4$•$5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) and H_2SO_4 (5.5 mL) in water (7.5 mL). The mixture was stirred at 0 °C for 45 min and allowed to warm up to room temperature where it stirred further for 1 h before CuCl (118 mg) was added. This mixture was stirred further at room temperature

for 16 h before it was diluted with brine and extracted with ether twice. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 2-chloro-5-ethylthiazole-4-carboxylate (*i.e.*, Cap-172, Step a) (175 mg, 85%) as an orange oil (80% pure) which was used directly in the next reaction. R_t = 1.99 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; found: 206.05.

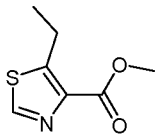
Cap-172

[00272] To a solution of methyl 2-chloro-5-ethylthiazole-4-carboxylate (175 mg) in $THF/H_2O/MeOH$ (20 mL/ 3 mL/ 12 mL) was added LiOH (305 mg, 12.76 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield Cap-172 (60 mg, 74%) as a red solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, *J* = 7.4 Hz), 1.23 (3 H, t, *J* = 7.5 Hz). R_t = 1.78 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; found: 191.99.

Cap-173



Cap-173, Step a



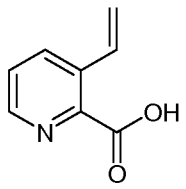
[00273] The following diazotization step was adapted from Barton, A. et al., *J.C.S. Perkin Trans I*, 159-164 (1982): A solution of $NaNO_2$ (150 mg, 2.17 mmol) in water (1.0 mL) was added dropwise to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol) in 50% H_3PO_2 (3.2 mL). The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature where it stirred further for 2h. After recooling to 0 °C, the mixture was treated slowly with a solution of NaOH

(85 mg) in water (10 mL). The mixture was then diluted with saturated $NaHCO_3$ solution and extracted twice with ether. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 5-ethylthiazole-4-carboxylate (*i.e.*, Cap-173, Step a) (134 mg, 78%) as an orange oil (85% pure) which was used directly in the next reaction. R_t = 1.58 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; found: 172.05.

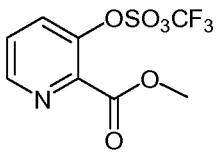
Cap-173

[00274] To a solution of methyl 5-ethylthiazole-4-carboxylate (134 mg) in THF/H_2O/MeOH (18 mL/ 2.7 mL/ 11 mL) was added LiOH (281 mg, 11.74 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield Cap-173 (90 mg, 73%) as an orange solid which was used without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 12.74-13.04 (1 H, m), 3.20 (2 H, q, J = 7.3 Hz), 1.25 (3 H, t, J = 7.5 Hz). R_t = 1.27 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_6H_8NO_2S$: 158.03; found: 158.04.

Cap-174



Cap-174, Step a



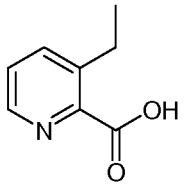
[00275] Triflic anhydride (5.0 g, 18.0 mmol) was added dropwise to a cold (0 °C) solution of methyl 3-hydroxypicolinate (2.5 g, 16.3 mmol) and TEA (2.5 mL, 18.0 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at 0 °C for 1h before it was allowed to warm up to room temperature where it stirred for an additional 1 h. The mixture was then

quenched with saturated $NaHCO_3$ solution (40 mL) and the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to give methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e.*, Cap-174, Step a) (3.38 g, 73%) as a dark brown oil (>95% pure) which was used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, *J* = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). R_t = 1.93 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; found: 286.08.

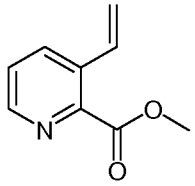
Cap-174

[00276] To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (570 mg, 2.0 mmol) in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C overnight before a saturated solution of KF (20 mL) was added to the reaction mixture at room temperature. This mixture was stirred for 4 h before it was filtered through CELITE® and the pad of CELITE® was washed with ethyl acetate. The aqueous phase of the filtrate was then separated and concentrated down *in vacuo*. The residue was treated with 4*N* HCl in dioxanes (5 mL) and the resulting mixture was extracted with methanol, filtered and evaporated to afford Cap-174 (260 mg) as a green solid which was slightly contaminated with inorganic salts but was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.21 (1 H, d, *J* = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, *J* = 7.7, 4.8 Hz), 6.98 (1 H, dd, *J* = 17.9, 11.3 Hz), 5.74 (1 H, dd, *J* = 17.9, 1.5 Hz), 5.20 (1 H, d, *J* = 11.0 Hz). R_t = 0.39 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_8NO_2$: 150.06; found: 150.07.

Cap-175

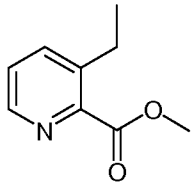


Cap-175, Step a



[00277] To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e.*, Cap-174, Step a) (570 mg, 2.0 mmol), an intermediate in the preparation of Cap-174, in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C for 4 h before the solvent was removed *in vacuo*. The residue was taken up in acetonitrile (50 mL) and hexanes (50 mL) and the resulting mixture was washed twice with hexanes. The acetonitrile layer was then separated, filtered through CELITE®, and evaporated. Purification of the residue by flash chromatography on a Horizon instrument (gradient elution with 25% ethyl acetate in hexanes to 65% ethyl acetate in hexanes) afforded methyl 3-vinylpicolinate (*i.e.*, Cap-175, Step a) (130 mg, 40%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, J = 4.6, 1.7 Hz), 7.94 (1 H, d, J = 7.7 Hz), 7.33-7.51 (2 H, m), 5.72 (1 H, d, J = 17.2 Hz), 5.47 (1 H, d, J = 11.0 Hz), 3.99 (3 H, s). R_t = 1.29 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; found: 164.06.

Cap-175, Step b

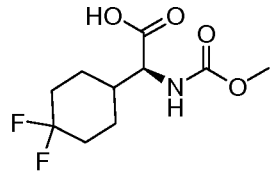


[00278] Palladium on carbon (10%, 25 mg) was added to a solution of methyl 3-vinylpicolinate (120 mg, 0.74 mmol) in ethanol (10 mL). The suspension was stirred at room temperature under an atmosphere of hydrogen for 1 h before it was filtered through CELITE® and the pad of CELITE® was washed with methanol. The filtrate was concentrated down to dryness to yield methyl 3-ethylpicolinate (*i.e.*, Cap-175, Step b) which was taken directly into the next reaction. R_t = 1.15 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; found: 166.09.

Cap-175

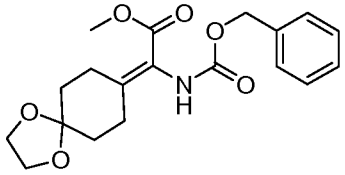
[00279] To a solution of methyl 3-ethylpicolinate in THF/H_2O/MeOH (5 mL/ 0.75 mL/ 3 mL) was added LiOH (35 mg, 1.47 mmol). The mixture was stirred at room temperature for 2 d before additional LiOH (80 mg) was added. After an additional 24 h at room temperature, the mixture was filtered and the solvent was removed *in vacuo*. The residue was then treated with 4*N* HCl in dioxanes (5 mL) and the resulting suspension was concentrated down to dryness to yield Cap-175 as a yellow solid which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47 (1 H, dd, J = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, J = 7.7, 4.8 Hz), 2.82 (2 H, q, J = 7.3 Hz), 1.17 (3 H, t, J = 7.5 Hz). R_t = 0.36 min (Cond.-MD1); LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; found: 152.10.

Cap-176



(S)-2-(4,4-Difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid

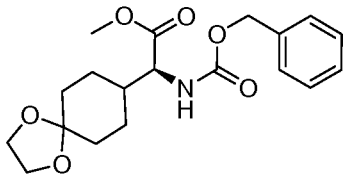
Cap-176, Step a



[00280] A solution of 1,4-dioxaspiro[4.5]decan-8-one (15 g, 96 mmol) in EtOAc (150 mL) was added to a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (21.21 g, 64.0 mmol) in 1,1,3,3-tetramethylguanidine (10.45 mL, 83 mmol) and EtOAc (150 mL). The resulting solution was the stirred at ambient temperature for 72 h and then it was diluted with EtOAc (25 mL). The organic layer was washed with 1N HCl (75 mL), H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified via BIOTAGE® (5% to 25 % EtOAc/Hexanes; 300g column). The combined fractions containing the product were then concentrated under vacuum and the residue was re-crystallized from hexanes/EtOAc

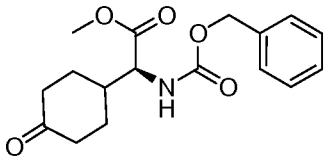
to give white crystals that corresponded to methyl 2-(benzyloxycarbonylamino)-2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (6.2 g) ^{1}H NMR (400 MHz, $CDCl_3$-d) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, br. s.), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, br. s.), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). LC (Cond. OL1): R_t = 2.89 min. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; found: 745.47.

Cap-176, Step b



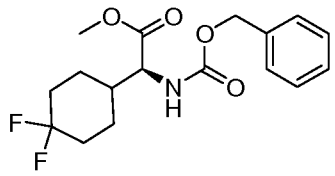
[00281] Ester Cap-176, Step b was prepared from alkene Cap-176, Step a according to the method of Burk, M.J. et al. (*J. Am. Chem. Soc.*, 117:9375-9376 (1995)) and references therein): A 500 mL high-pressure bottle was charged with alkene Cap-176, Step a (3.5 g, 9.68 mmol) in degassed MeOH (200 mL) under a blanket of N_2. The solution was then charged with (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene) rhodium (I) tetrafluoroborate (0.108 g, 0.194 mmol) and the resulting mixture was flushed with N_2 (3x) and charged with H_2 (3x). The solution was shaken vigorously under 70 psi of H_2 at ambient temperature for 72 h. The solvent was removed under reduced pressure and the remaining residue was taken up in EtOAc. The brownish solution was then filtered through a plug of Silica Gel and eluted with EtOAc. The solvent was concentrated under vacuum to afford a clear oil corresponding to ester Cap-176, Step b (3.4 g).^{1}H NMR (500 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). LC (Cond. OL1): R_t = 1.95 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; found: 364.27.

Cap-176, Step c



[00282] Ester Cap-176, Step b (4.78 g, 13.15 mmol) was dissolved in THF (15 mL) followed by sequential addition of water (10 mL), glacial acetic acid (26.4 mL, 460 mmol) and dichloroacetic acid (5.44 mL, 65.8 mmol). The resulting mixture was stirred for 72 h at ambient temperature, and the reaction was quenched by slow addition of solid Na_2CO_3 with vigorous stirring until the release of gas was no longer visible. Crude product was extracted into 10% ethyl acetate-dichloromethane and the organic layers were combined, dried ($MgSO_4$) filtered and concentrated. The resulting residue was purified via BIOTAGE® (0 to 30% EtOAc/Hex; 25 g column) to afford ketone Cap-176, Step c (3.86g) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd, *J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). LC (Cond. OL1): R_t = 1.66 min. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; found: 342.10.

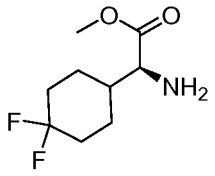
Cap-176, Step d



[00283] DEOXO-FLUOR® (3.13 mL, 16.97 mmol) was added to a solution of ketone Cap-176, Step c (2.71 g, 8.49 mmol) in CH_2Cl_2 (50 mL) followed by addition of a catalytic amount of EtOH (0.149 mL, 2.55 mmol). The resulting yellowish solution was stirred at rt overnight. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (25 mL) and the mixture was extracted with EtOAc (3X75 mL)). The combined organic layers were dried ($MgSO_4$), filtered and dried to give a yellowish oil. The residue was purified via BIOTAGE® chromatography (2% to 15% EtOAc/Hex; 90g column) and a white solid corresponding to the difluoro amino acid difluoride Cap-176, Step d (1.5 g) was recovered. ^{1}H NMR (400 MHz,, $CDCl_3$-d) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). ^{19}F NMR (376 MHz, $CDCl_3$-d) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). LC (Cond.

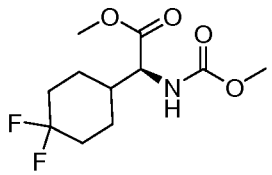
OL1): R_t = 1.66 min. LC-MS: Anal. Calcd. for $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; found: 705.18.

Cap-176, Step e



[00284] Difluoride Cap-176, Step d (4 g, 11.72 mmol) was dissolved in MeOH (120 mL) and charged with Pd/C (1.247 g, 1.172 mmol). The suspension was flushed with N_2 (3x) and the reaction mixture was placed under 1 atm of H_2 (balloon). The mixture was stirred at ambient temperature for 48 h. The suspension was then filtered though a plug of CELITE® and concentrated under vacuum to give an oil that corresponded to amino acid Cap-176, Step e (2.04 g) and that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, br. s.), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). LC (Cond. OL2): R_t = 0.95 min. LC-MS: Anal. Calcd. for $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; found: 415.40.

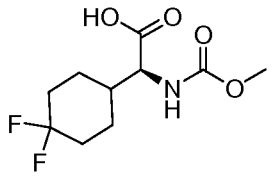
Cap-176, Step f



[00285] Methyl chloroformate (1.495 mL, 19.30 mmol) was added to a solution of amino acid Cap-176, Step e (2 g, 9.65 mmol) and DIEA (6.74 mL, 38.6 mmol) in CH_2Cl_2 (100 mL). The resulting solution was stirred at rt for 3 h and volatiles were removed under reduced pressure. The residue was purified via BIOTAGE® (0% to 20% EtOAc/Hex; 90g column). A clear oil that solidified upon standing under vacuum and corresponding to carbamate Cap-176, Step f (2.22 g) was recovered. ^{1}H NMR (500 MHz,

$CDCl_3$-d) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3 H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). ^{19}F NMR (471 MHz, $CDCl_3$-d) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). ^{13}C NMR (126 MHz, $CDCl_3$-d) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, br. s.), 52.48 (1 C, br. s.), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d, *J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). LC (Cond. OL1): R_t = 1.49 min. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; found: 288.03.

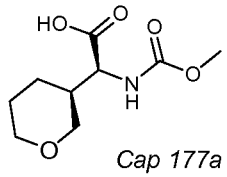
Cap-176



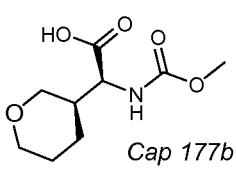
(S)-2-(4,4-Difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid

[00286] A solution of LiOH (0.379 g, 15.83 mmol) in water (25 mL) was added to a solution of carbamate Cap-176, Step f (2.1 g, 7.92 mmol) in THF (75 mL) and the resulting mixture was stirred at ambient temperature for 4 h. THF was removed under vacuum and the remaining aqueous phase was acidified with 1N HCl solution (2 mL) and then extracted with EtOAc (2 X 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a white foam corresponding to Cap-176 (1.92 g). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.73 (1 H, s), 7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). LC (Cond. OL2): R_t = 0.76 min. LC-MS: Anal. Calcd. for $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; found: 250.10.

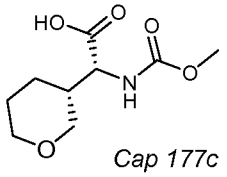
Cap-177a-d



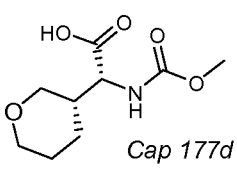
Cap 177a



Cap 177b

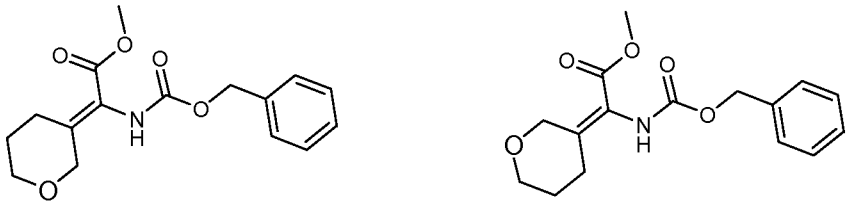


Cap 177c



Cap 177d

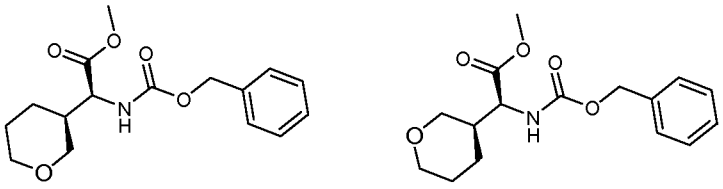
Cap-177a-d, Step a



[00287] 1,1,3,3-Tetramethylguanidine (0.985 mL, 7.85 mmol) was added to a stirred solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (2.0 g, 6.0 mmol) in EtOAc (40 mL) and the mixture was stirred at rt under N_2 for 10 min. Then dihydro-2H-pyran-3(4H)-one [23462-75-1] (0.604 g, 6.04 mmol) was added and the mixture was stirred at rt for 16 h. The reaction mixture was then cooled in freezer for 10 min and neutralized with aq. citric acid (1.5 g in 20 mL water). The two phases were partitioned and the organic layer was washed with 0.25 N aq.HCl and brine, and then dried ($MgSO_4$) and concentrated to a colorless oil. The crude material was purified by flash silica chromatography (loading solvent: DCM, eluted with EtOAc/Hexanes, gradient from 20% to 30% EtOAc) to yield two isomeric products: The first eluted product was (Z)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (490 mg) (white solid), and the second was (E)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (433 mg) (white solid). LC-MS retention time 1.398 min (for Z-isomer) and 1.378min (for E-isomer); m/z 304.08 (for Z-isomer) and 304.16 (for E-isomer) (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) (for Z-isomer) δ ppm 7.30 - 7.44 (m, 5 H), 6.18 (br. s., 1 H), 5.10 - 5.17 (m, 2 H), 4.22 (s, 2 H), 3.78 (br. s., 3 H), 2.93 - 3.02 (m, 2 H), 1.80 (dt, *J*=11.7, 5.8 Hz, 2 H), 1.62 (s, 2 H). ^{1}H NMR (400 MHz, chloroform-d) (for E-isomer) δ ppm 7.31 - 7.44 (m, 5 H), 6.12 (br. s., 1 H), 5.13 - 5.17 (m, 2 H), 4.64 (br. s., 2 H), 3.70 - 3.82 (m, 5 H), 2.49 (t, *J*=6.5 Hz, 2 H), 1.80 (br. s., 2 H).

(Note: the absolute regiochemistry was determined by ^{1}H NMR shifts and coupling constants).

Cap-177a-d, Step b



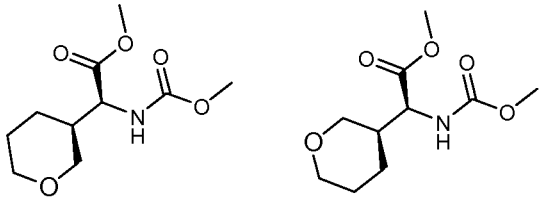
[00288] (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene)-rhodium(I)tetrafluoroborate (28.2 mg, 0.051 mmol) was added to a stirred solution of (Z)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate (310 mg, 1.015 mmol) in MeOH (10 mL) and the mixture was vacuum flushed with N_2, followed by H_2, and then the reaction was stirred under H_2 (60 psi) at rt for 2d. The reaction mixture was concentrated and the residue was purified by flash silica chromatography (loading solvent: DCM, eluted with 20% EtOAc in hexanes) to yield (S)-methyl 2-(benzyloxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (204 mg) as clear colorless oil. LC-MS retention time 1.437 min; m/z 307.89 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.30 - 7.46 (m, 5 H), 5.32 (d, *J*=8.8 Hz, 1 H), 5.12 (s, 2 H), 4.36 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.98 (m, 2 H), 3.77 (s, 3 H), 3.28 - 3.37 (m, 1 H), 3.23 (dd, *J*=11.3, 10.5 Hz, 1 H), 2.04 - 2.16 (m, 1 H), 1.61 - 1.75 (m, 3 H), 1.31 - 1.43 (m, 1 H).

[00289] The other stereoisomer ((E)-methyl 2-(benzyloxycarbonylamino)-2-(2H-pyran-3(4H,5H,6H)-ylidene)acetate) (360 mg, 1.18 mmol) was reduced in a similar manner to yield (S)-methyl 2-(benzyloxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate (214 mg) as clear colorless oil. LC-MS retention time 1.437 min; m/z 308.03

(MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.30 - 7.44 (m, 5 H), 5.31 (d, *J*=9.0 Hz, 1 H), 5.12 (s, 2 H), 4.31 (dd, *J*=8.7, 6.9 Hz, 1 H), 3.80 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.37 (td, *J*=10.8, 3.5 Hz, 1 H), 3.28 (dd, *J*=11.3, 9.8 Hz, 1 H), 1.97 - 2.10 (m, 1 H), 1.81 (d, *J*=11.5 Hz, 1 H), 1.61 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

[00290] The individual enantiomers of Cap-177a, Step b (Cap-177c, Step b) and Cap-177b, Step b (Cap-177d, Step b) were prepared in the same manner and in similar yields utilizing (-)-1,2-Bis((2R,5R)-2,5-dimethylphospholano)ethane (cyclooctadiene)-rhodium(I)tetrafluoroborate as the hydrogenation catalyst for the olefin reductions of the individual stereoisomer starting materials.

Cap-177a and Cap-177b, Step c



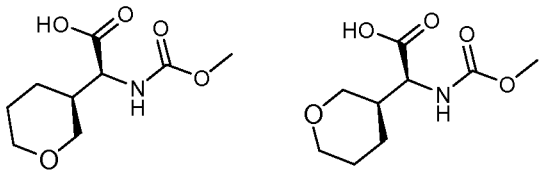
[00291] 10% Pd/C (69.3 mg, 0.065 mmol) was added to a solution of (S)-methyl 2-(benzyloxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (200 mg, 0.651 mmol) and dimethyl dicarbonate [4525-33-1] (0.104 mL, 0.976 mmol) in MeOH (10 mL). The reaction mixture was vacuum flushed with N_2, followed by H_2, and then the reaction was stirred under H_2 (55 psi) at rt for 5 h. The reaction mixture was filtered through CELITE®/silica pad and the filtrate was concentrated to a colorless oil. The crude oil was purified by flash silica chromatography (loading solvent: DCM, eluted with 30% EtOAc in hexanes) to yield product (S)-methyl 2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (132 mg) as colorless oil. LC-MS retention time 0.92

min; m/z 231.97 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.24 (d, *J*=8.5 Hz, 1 H), 4.34 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.97 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.29 - 3.38 (m, 1 H), 3.23 (dd, *J*=11.2, 10.4 Hz, 1 H), 2.03 - 2.14 (m, 1 H), 1.56 - 1.75 (m, 3 H), 1.32 - 1.43 (m, 1 H).

[00292] Another diastereomer ((S)-methyl 2-(benzyloxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate) was transformed in a similar manner to yield (S)-methyl 2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate as clear colorless oil. LC-MS retention time 0.99 min; m/z 231.90 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.25 (d, *J*=8.0 Hz, 1 H), 4.29 (dd, *J*=8.4, 7.2 Hz, 1 H), 3.82 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.37 (td, *J*=10.8, 3.3 Hz, 1 H), 3.28 (t, *J*=10.5 Hz, 1 H), 1.96 - 2.08 (m, 1 H), 1.81 (dd, *J*=12.9, 1.6 Hz, 1 H), 1.56 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

[00293] The individual enantiomers of Cap-177a, Step c (Cap-177c, Step c) and Cap-177b, Step c (Cap-177d, Step c) were prepared in a similar manner and is similar yields using the appropriate starting materials from Cap-177a-d, Step b.

Cap-177a and Cap-177b, Step d



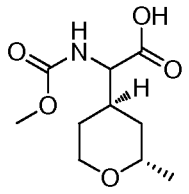
[00294] To a solution of (S)-methyl 2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetate (126 mg, 0.545 mmol) in THF (4 mL) stirring at rt was added a solution of 1M LiOH (1.090 mL, 1.090 mmol) in water. The reaction was stirred at rt for 3h, neutralized with 1M HCl (1.1 mL) and extracted with EtOAc (3x 10 mL). The organics were dried, filtered and concentrated to yield (S)-2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetic acid (Cap-177a) (125 mg) as a clear colorless oil. LC-MS retention time 0.44 min; m/z 218.00 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 5.28 (d, *J*=8.8 Hz, 1 H), 4.38 (dd, *J*=8.7, 5.6 Hz, 1 H), 3.96 - 4.04 (m, 1 H), 3.91 (d, *J*=11.0 Hz, 1 H), 3.71 (s, 3 H), 3.33 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 1 H), 2.10 - 2.24 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.63 - 1.71 (m, 2 H), 1.35 - 1.49 (m, 1 H).

[00295] Another diastereomer ((S)-methyl 2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetate) was transformed in a similar manner to yield (S)-2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetic acid (Cap-177b) as clear colorless oil. LC-MS retention time 0.41 min; m/z 217.93 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a PHENOMENEX® Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where Solvent A was 5% MeOH / 95% H_2O / 10 mM ammonium acetate and Solvent B

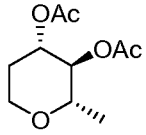
was 5% H_2O / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a MICROMASS® Platform for LC in electrospray mode. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 6.18 (br. s., 1 H), 5.39 (d, *J*=8.5 Hz, 1 H), 4.27 - 4.37 (m, 1 H), 3.82 - 3.96 (m, 2 H), 3.72 (s, 3 H), 3.42 (td, *J*=10.8, 3.3 Hz, 1 H), 3.35 (t, *J*=10.4 Hz, 1 H), 2.01 - 2.18 (m, 1 H), 1.90 (d, *J*=11.8 Hz, 1 H), 1.59 - 1.76 (m, 2 H), 1.40 - 1.54 (m, 1 H).

[00296] The individual enantiomers of Cap-177a (Cap-177c) and Cap-177b (Cap-177d) were prepared in a similar manner and is similar yields using the appropriate starting materials from Cap-177a-d, Step c.

Cap-178

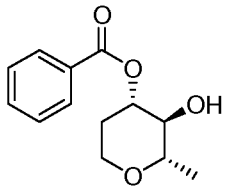


Cap-178, Step a



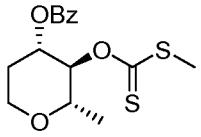
[00297] To a solution of (2S,3S,4S)-2-methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (5 g, 23.34 mmol) in 20 mL of MeOH in a hydrogenation tank was added Pd/C (150 mg, 0.141 mmol). The resulting mixture was hydrogenated at 40 psi on Parr Shaker for 1 hour. The mixture was then filtered and the filtrate was concentrated to afford Cap-178, Step a (5.0 g) as a clear oil, which solidified while standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.85 - 4.94 (1 H, m), 4.69 (1 H, t, *J*=9.46 Hz), 3.88 - 3.94 (1 H, m), 3.44 (1 H, td, *J*=12.21, 1.83 Hz), 3.36 (1 H, dq, *J*=9.42, 6.12 Hz), 2.03 - 2.08 (1 H, m), 2.02 (3 H, s), 2.00 (3 H, s), 1.70 - 1.80 (1 H, m), 1.16 (3 H, d, *J*=6.10 Hz).

Cap-178, Step b



[00298] To a solution of Cap-178, Step a (5.0 g, 23 mmol) in 50 mL of MeOH was added several drops of sodium methoxide. After stirring at room temperature for 30 min, sodium methoxide (0.1 mL, 23.12 mmol) was added and the solution was stirred at room temperature overnight. The solvent was then removed under vacuum. The residue was diluted with benzene and concentrated to afford the corresponding diol as a yellow solid. The solid was dissolved in 50 mL of pyridine and to this solution at -35 °C was added benzoyl chloride (2.95 mL, 25.4 mmol) dropwise. The resulting mixture was stirred at -35 °C for 1 hour then at room temperature overnight. The mixture was diluted with Et_2O and washed with water. The aqueous layer was extracted with EtOAc (2X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 5%-15% EtOAc/Hex) to afford Cap-178, Step b (4.5 g) as clear oil which slowly crystallized upon prolonged standing. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{16}NaO_4$ 259.09; found 259.0; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.02 - 8.07 (2 H, m), 7.55 - 7.61 (1 H, m), 7.45 (2 H, t, *J*=7.78 Hz), 5.01 (1 H, ddd, *J*=11.44, 8.70, 5.49 Hz), 3.98 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.54 (1 H, td, *J*=12.36, 2.14 Hz), 3.41 (1 H, t, *J*=9.00 Hz), 3.31 - 3.38 (1 H, m), 2.13 - 2.19 (1 H, m), 1.83 - 1.94 (1 H, m), 1.36 (3 H, d, *J*=5.80 Hz).

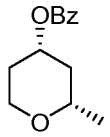
Cap-178, Step c



[00299] To a mixture of NaH (1.143 g, 28.6 mmol) (60% in mineral oil) in 6 mL of CS_2 was added Cap-178, Step b (4.5 g, 19 mmol) in 40 mL of CS_2 dropwise over 15 min. The resulting mixture was stirred at room temperature for 30 min. The mixture turned light orange with some solid. MeI (14.29 mL, 229 mmol) was then added dropwise over 20 min. The mixture was then stirred at room temperature overnight. The reaction was carefully quenched with saturated NH_4Cl solution. The mixture was extracted with

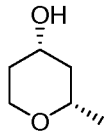
EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 6% EtOAc/Hex) to afford Cap-178, Step c (3.13 g) as clear oil. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{18}NaO_4S_2$ 349.05; found 349.11; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 - 8.00 (2 H, m), 7.50 - 7.58 (1 H, m), 7.41 (2 H, t, *J*=7.78 Hz), 5.96 (1 H, t, *J*=9.46 Hz), 5.28 (1 H, ddd, *J*=11.37, 9.38, 5.49 Hz), 4.02 (1 H, ddd, *J*=11.98, 4.96, 1.68 Hz), 3.54 - 3.68 (2 H, m), 2.48 (3 H, s), 2.31 (1 H, dd), 1.88 - 1.99 (1 H, m), 1.28 (3 H, d).

Cap-178, Step d



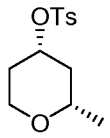
[00300] To a mixture of Cap-178, Step c (3.13 g, 9.59 mmol) and AIBN (120 mg, 0.731 mmol) in 40 mL of benzene at 80 °C was added tri-n-butyltin hydride (10.24 mL, 38.4 mmol). The resulting mixture was stirred at reflux temperature for 20 min then cooled to room temperature. The mixture was diluted with diethyl ether and 100 mL of KF (10 g) aqueous solution was added and the mixture was stirred vigorously for 30 min. The two layers were then separated and the aqueous phase was extracted with EtOAc (2X). The organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, deactivated with 3% Et_3N in Hexanes and flushed with 3% Et_3N in Hexanes to remove tributyltin derivative and then eluted with 15% EtOAc/Hex) to afford Cap-178, Step d (1.9 g) as clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.98 - 8.07 (2 H, m), 7.52 - 7.58 (1 H, m), 7.43 (2 H, t, *J*=7.63 Hz), 5.08 - 5.17 (1 H, m), 4.06 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.50 - 3.59 (2 H, m), 2.08 - 2.14 (1 H, m), 1.99 - 2.06 (1 H, m), 1.69 - 1.80 (1 H, m), 1.41 - 1.49 (1 H, m), 1.24 (3 H, d, *J*=6.10 Hz).

Cap-178, Step e



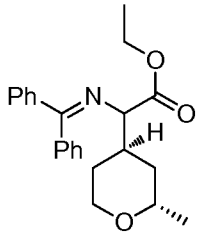
[00301] To a mixture of Cap-178, Step d (1.9 g, 8.63 mmol) in 10 mL of MeOH was added sodium methoxide (2 mL, 4.00 mmol) (2 M in methanol). The resulting mixture was stirred at room temperature for 5 hours. The solvent was removed under vacuum. The mixture was neutralized with saturated NH_4Cl solution and extracted with EtOAc (3X). The organic layers were dried with $MgSO_4$ and concentrated to afford Cap-178, Step e (0.8 g) as clear oil. The product was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.01 (1 H, ddd, *J*=11.80, 5.02, 1.76 Hz), 3.73 - 3.83 (1 H, m), 3.36 - 3.46 (2 H, m), 1.92 - 2.00 (1 H, m), 1.88 (1 H, m), 1.43 - 1.56 (1 H, m), 1.23 (3 H, d), 1.15 - 1.29 (1 H, m).

Cap-178, Step f



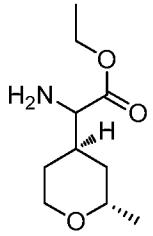
[00302] Tosyl-Cl (2.63 g, 13.77 mmol) was added to a solution of Cap-178, Step e (0.8 g, 6.89 mmol) and pyridine (2.23 mL, 27.5 mmol) in 100 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 3 days. 10 mL of water was then added into the reaction mixture and the mixture was stirred at room temperature for an hour. The two layers were separated and the organic phase was washed with water and 1 N HCl aq. solution. The organic phase was dried with $MgSO_4$ and concentrated to afford Cap-178, Step f (1.75 g) as a light yellow solid. The product was used in the next step without further purification. Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}O_4S$ 271.10; found 270.90; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=7.93 Hz), 4.53 - 4.62 (1 H, m), 3.94 (1 H, ddd, *J*=12.13, 4.96, 1.83 Hz), 3.29 - 3.41 (2 H, m), 2.45 (3 H, s), 1.90 - 1.97 (1 H, m), 1.79 - 1.85 (1 H, m), 1.64 - 1.75 (1 H, m), 1.38 - 1.48 (1 H, m), 1.17 (3 H, d, *J*=6.10 Hz).

Cap-178, Step g



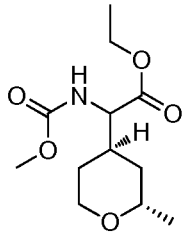
[00303] To a microwave tube was placed ethyl 2-(diphenylmethyleneamino)acetate (1.6 g, 5.92 mmol) and Cap-178, Step f (1.6 g, 5.92 mmol). 10 mL of toluene was added. The tube was sealed and LiHMDS (7.1 mL, 7.10 mmol) (1 N in toluene) was added dropwise under N_2. The resulting dark brown solution was heated at 100 °C under microwave radiation for 6 hours. To the mixture was then added water and the mixture was extracted with EtOAc (3X). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated to afford a diastereomeric mixture of Cap-3, Step g (3.1 g) as an orange oil. The crude mixture was submitted to the next step without separation. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{28}NO_3$ 366.21; found 366.3.

Cap-178, Step h



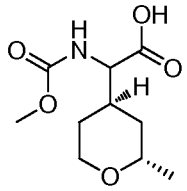
[00304] To a solution of the diastereomeric mixture of ethyl Cap-178, Step g in 20 mL of THF was added HCl (30 ml, 60.0 mmol) (2 N aqueous). The resulting mixture was stirred at room temperature for 1 hour. The mixture was extracted with EtOAc and the aqueous layer was concentrated to afford an HCl salt of Cap-178, Step h (1.9 g) as an orange oil. The salt was used in the next step without further purification. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{20}NO_3$ 202.14; found 202.1.

Cap-178, Step i



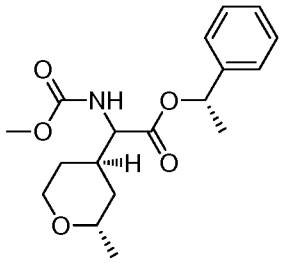
[00305] A solution of 1.9 g Cap-178, Step h (HCl salt), DiPEA (4.19 mL, 24.0 mmol) and methyl chloroformate (1.24 mL, 16.0 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature for 1 hour. The mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 0-20% EtOAc/Hex) to afford Cap-178, Step i (1.1 g) as a yellow oil. Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{21}NNaO_5$ 282.13; found 282.14; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.16 (1 H, br. s.), 4.43 - 4.58 (1 H, m), 4.17 - 4.28 (2 H, m), 3.89 - 4.03 (1 H, m), 3.72 - 3.78 (2 H, m), 3.67 - 3.72 (3 H, m), 2.07 - 2.19 (1 H, m), 1.35 - 1.77 (4 H, m), 1.30 (3 H, td, *J*=7.09, 2.89 Hz), 1.19 (3 H, d, *J*=6.53 Hz).

Cap-178, Step j



[00306] To a mixture of Cap-178, Step i (1.1 g, 4.2 mmol) in 5 mL of THF and 2 mL of water was added LiOH (6.36 mL, 12.7 mmol) (2 N aq.). The resulting mixture was stirred at room temperature overnight. The mixture was then neutralized with 1 N HCl aq. and extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-178, Step j (0.8 g) as a clear oil. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; found 232.1; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.20 (1 H, d, *J*=8.28 Hz), 4.54 (1 H, t, *J*=8.16 Hz), 3.95 - 4.10 (1 H, m), 3.66 - 3.85 (5 H, m), 2.15 - 2.29 (1 H, m), 1.41 - 1.85 (4 H, m), 1.23 (3 H, dd, *J*=6.53, 1.76 Hz).

Cap-178, Step k



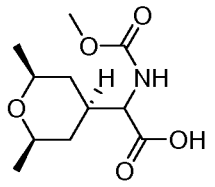
[00307] To a solution of Cap-178, Step j (240 mg, 1.04 mmol), (S)-1-phenylethanol (0.141 mL, 1.142 mmol) and EDC (219 mg, 1.14 mmol) in 10 mL of CH_2Cl_2 was added DMAP (13.95 mg, 0.114 mmol). The resulting solution was stirred at room temperature overnight and the solvent was removed under vacuum. The residue was taken up into EtOAc, washed with water, dried with $MgSO_4$ and concentrated. The crude product was purified by chromatography (silica gel, 0-15% EtOAc/Hexanes) to afford Cap-178, Step k as a mixture of two diastereomers. The mixture was separated by chiral HPLC (CHIRALPAK® AS column, 21 x 250 mm, 10 um) eluting with 90% 0.1%diethylamine/Heptane-10% EtOH at 15 mL/min to afford Cap-178, Step k stereoisomer 1 (eluted first) and Cap-178, Step k stereoisomer 2 (eluted second) as white solids. The stereochemistry of the isomers was not assigned.

[00308] Cap-178, Step k stereoisomer 1 (130 mg): LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{25}NNaO_5$ 358.16; found 358.16; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.28 - 7.38 (5 H, m), 5.94 (1 H, q, *J*=6.71 Hz), 5.12 (1 H, d, *J*=9.16 Hz), 4.55 (1 H, t, *J*=9.00 Hz), 3.72 - 3.81 (1 H, m), 3.67 (3 H, s), 3.60 - 3.70 (2 H, m), 1.98 - 2.08 (1 H, m), 1.59 (3 H, d, *J*=6.71 Hz), 1.38 - 1.47 (2 H, m), 1.30 (2 H, t, *J*=5.34 Hz), 0.93 (3 H, d, *J*=6.41 Hz).

Cap-178, Stereoisomer 1

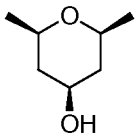
[00309] To a solution of Cap-178, Step k stereoisomer 1 ((S)-2-(methoxycarbonylamino)-2-((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)acetic acid) (150 mg, 0.447 mmol) in 10 mL of EtOH was added Pd/C (20 mg, 0.188 mmol) and the mixture was hydrogenated on Parr shaker at 40 psi overnight. The mixture was then filtered and the filtrate was concentrated to afford Cap-178, stereoisomer 1 (100 mg) as a sticky white solid. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; found 232.1; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.14 - 5.27 (1 H, m), 4.51 (1 H, t, *J*=8.39 Hz), 3.90 - 4.07 (1 H, m), 3.60 - 3.83 (5 H, m), 2.06 - 2.27 (1 H, m), 1.45 - 1.77 (4 H, m), 1.21 (3 H, d, *J*=6.41 Hz).

Cap-179 (Enantiomer-1 and Enantiomer-2)



179 stereoisomer 1
179 stereoisomer 2

Cap-179, Step a

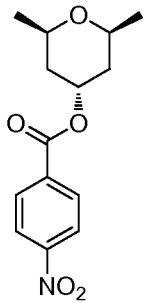


[00310] 2,6-Dimethyl-4H-pyran-4-one (10 g, 81 mmol) was dissolved in ethanol (125 mL) and Pd/C (1 g, 0.94 mmol) was added. The mixture was hydrogenated in a Parr shaker under H_2 (0.325 g, 161 mmol) (70 psi) at room temperature for 12 hrs. The catalyst was filtered through a pad of CELITE® and washed with ethanol. The filtrate was concentrated in vacuum and he residue was purified via BIOTAGE® (2% to 25 % EtOAc/Hex; 160g column). Two fractions of clear oils were isolated. The first eluting one corresponded to (2R,6S)-2,6-dimethyldihydro-2H-pyran-4(3H)-one (1.8 g) while the second one corresponded to Cap-179, Step a (1.8 g).

[00311] (2R,6S)-2,6-Dimethyldihydro-2H-pyran-4(3H)-one data: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.69 (2 H, ddd, *J*=11.29, 5.95, 2.29 Hz), 2.24 - 2.36 (2 H, m), 2.08 - 2.23 (2 H, m), 1.18 - 1.34 (6 H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 206.96 (1 C, br. s.), 72.69 (2 C, s), 48.70 (2 C, s), 21.72 (2 C, s).

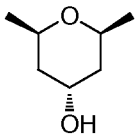
[00312] Cap-179, Step a data: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.69 - 3.78 (1 H, m), 3.36 - 3.47 (2 H, m), 2.10 (1 H, br. s.), 1.88 (2 H, dd, *J*=12.05, 4.73 Hz), 1.19 (6 H, d, *J*=6.10 Hz), 1.10 (2 H, q, *J*=10.70 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 71.44 (2 C, s), 67.92 (1 C, s), 42.59 (2 C, s), 21.71 (2 C, s).

Cap-179, Step b



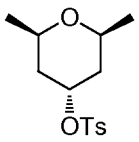
[00313] DEAD (2.311 mL, 14.59 mmol) was added drop wise to a solution of Cap-179, Step a (0.38 g, 2.92 mmol), 4-nitrobenzoic acid (2.195 g, 13.14 mmol) and Ph_3P (3.83 g, 14.59 mmol) in benzene (25 mL). Heat evolution was detected and the resulting amber solution was stirred at ambient temperature for 6 h. Solvent was removed under reduced pressure and the residue was purified via BIOTAGE® (0 to 15% EtOAc/Hex; 80g column). A white solid corresponding to Cap-179, Step b (0.77 g) was isolated. LC-MS: Anal. Calcd. for $[M]^+$ $C_{14}H_{17}NO_5$: 279.11; found 279.12. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.27 - 8.32 (2 H, m), 8.20 - 8.24 (2 H, m), 5.45 (1 H, quin, *J*=2.82 Hz), 3.92 (2 H, dqd, *J*=11.90, 6.10, 6.10, 6.10, 1.53 Hz), 1.91 (2 H, dd, *J*=14.80, 2.29 Hz), 1.57 (3 H, dt, *J*=14.65, 3.05 Hz), 1.22 (6 H, d, *J*=6.10 Hz).

Cap-179, Step c



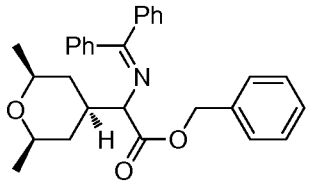
[00314] A solution LiOH (0.330 g, 13.8 mmol) in water (8 mL) was added to a solution of Cap-179, Step b (0.77 g, 2.76 mmol) in THF (30 mL) and the resulting mixture was stirred at ambient temperature for 16 h. THF was removed under reduced pressure and the aqueous layer was diluted with more water (20 mL) and extracted with EtOAc (3 X 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. An oily residue with a white solid was recovered. The mixture was triturated with hexanes and the solid was filtered off to yield a clear oil corresponding to Cap-179, Step c (0.34 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.21 (1 H, quin, *J*=2.82 Hz), 3.87 - 3.95 (2 H, m), 1.72 (1 H, br. s.), 1.63 (2 H, dd, *J*=14.34, 2.14 Hz), 1.39 - 1.47 (2 H, m), 1.17 (6 H, d, *J*=6.41 Hz).

Cap-179, Step d



[00315] p-Tosyl chloride (3.98 g, 20.89 mmol) was added to a solution of Cap-179, Step c (1.36 g, 10.5 mmol) and Pyridine (3.38 mL, 41.8 mmol) in CH_2Cl_2 (150 mL) at room temperature and stirred for 24h and then concentrated to a yellow oil. The remaining residue was added to pyridine (20 mL) and water (30 mL) and the resulting mixture was stirred at ambient temperature for 1 1/2 h. The mixture was extracted with Et_2O (75 mL) and the separated organic layer was the washed thoroughly with 1 N aq. HCl (4 X 50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated. A white solid corresponding to Cap-179, Step d (2.2 g) was isolated. LC-MS: Anal. Calcd. for $[2M+H]^+$ $C_{28}H_{41}O_8S_2$: 569.22; found 569.3. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.35 (2 H, d, *J*=8.03 Hz), 4.89 (1 H, quin, *J*=2.82 Hz), 3.77 - 3.88 (2 H, m), 2.46 (3 H, s), 1.77 (2 H, dd, *J*=14.93, 2.89 Hz), 1.36 (2 H, ddd, *J*=14.31, 11.54, 2.76 Hz), 1.13 (6 H, d, *J*=6.27 Hz).

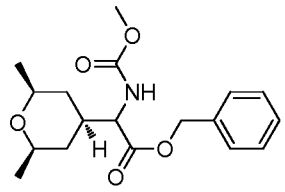
Cap-179, Step e



[00316] LiHMDS (4.30 mL, 4.30 mmol) was added to a solution of Cap-179, Step d (1.02 g, 3.59 mmol) and benzyl 2-(diphenylmethyleneamino)acetate (1.181 g, 3.59 mmol) in toluene (25 mL) at room temperature in a sealed microwave vial and the resulting mixture was then stirred for 5 h at 100 °C under microwave radiation. The reaction was quenched with water (10 mL), extracted with EtOAc, washed with water, dried over $MgSO_4$, filtrated, and concentrated in vacuum. The residue was purified via BIOTAGE® (0% to 6% EtOAc/Hex; 80g column) and a yellow oil corresponding to Cap-179, Step e (1.2 g) was isolated. Anal. Calcd. for $[2M+Na]^+$ $C_{58}H_{62}N_2NaO_6$: 905.45; found 905.42. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.70 (4 H, m), 7.29 - 7.44 (29 H, m), 7.06 (4 H, dd, *J*=7.65, 1.63 Hz), 5.18 (2 H, d, *J*=2.01 Hz), 3.89 (2 H, d, *J*=6.53 Hz), 3.79 - 3.87 (1 H,

m), 3.46 (5 H, dquind, *J*=11.26, 5.87, 5.87, 5.87, 5.87, 1.88 Hz), 2.47 (2 H, s), 2.35 - 2.46 (2 H, m), 1.78 (1 H, dd, *J*=14.81, 3.01 Hz), 1.62 - 1.65 (1 H, m), 1.61 (2 H, s), 1.36 - 1.43 (3 H, m), 1.19 (7 H, d, *J*=6.27 Hz), 1.14 (11 H, dd, *J*=6.15, 2.89 Hz), 0.86 - 0.96 (3 H, m).

Cap-179, Step f (Enantiomer-1 and Enantiomer-2)



[00317] Cap-179, Step e (2.08 g, 4.71 mmol) was dissolved in THF (100 mL) and treated with 2 N HCl (9.42 mL, 18.84 mmol). The resulting clear solution was stirred at ambient temperature for 4 h and then THF was removed under reduced pressure. The remaining aqueous layer was extracted with hexanes (3 X 20 ml) and after diluting with H_2O (20 mL), the aqueous phase was basified with 1 N NaOH to pH = 10 and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was taken up in CH_2Cl_2 (100 mL) and charged with DIEA (2.468 mL, 14.13 mmol) and methyl chloroformate (0.401 mL, 5.18 mmol). The resulting solution was stirred at ambient temperature for 2 h. The reaction mixture was quenched with water (10 mL) and the organic layer was removed under reduced pressure. The aqueous layer was then extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified via BIOTAGE® (10% EtOAc/Hex; 25 g column). A clear colorless oil corresponding to Cap-179, Step f (1.05 g) was recovered. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{26}NO_5$: 336.18; found 336.3. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.40 (5 H, m), 5.26 (1 H, d, *J*=8.24 Hz), 5.13 - 5.24 (2 H, m), 4.36 (1 H, dd, *J*=8.85, 4.88 Hz), 3.68 (3 H, s), 3.32 - 3.46 (2 H, m), 2.02 - 2.14 (1 H, m), 1.52 (1 H, d, *J*=12.82 Hz), 1.32 (1 H, d, *J*=12.51 Hz), 1.11 - 1.18 (6 H, m), 0.89 - 1.07 (2 H, m).

[00318] A chiral SFC method was developed to separate the racemic mixture by using 12% methanol as the modifier on a CHIRALPAK® AD-H column (30 x 250mm, 5μm) (Temp = 35 °C, Pressure = 150 bar, Wavelength = 210 nm, Flow rate = 70 mL/min for 8 min, Solvent A = CO_2, Solvent B = MeOH). The two separated isomers, Cap-179 Step f

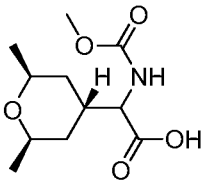
(Enantiomer-1) (first eluting) and Cap-179 Step f (Enantiomer-2) (second eluting) exhibited the same analytical data as the corresponding mixture (see above).

Cap-179 (Enantiomer-1 and Enantiomer-2)

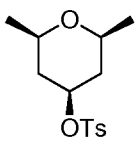
[00319] Cap-179 Step f (Enantiomer-1) (0.35 g, 1.044 mmol) was dissolved in MeOH (50 mL) in a Parr bottle and charged with Pd/C (0.111 g, 1.044 mmol). The suspension was then placed in a Parr shaker and the mixture was flushed with N_2 (3X), placed under 40 psi of H_2 (2.104 mg, 1.044 mmol) and shaken at room temperature for 2 h. The catalyst was filtered off through a pad of CELITE® and the solvent was removed under reduced pressure, to yield an amber solid corresponding to Cap-179 Enantiomer-1 (0.25 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.74 (4 H, br. s.), 7.35 (4 H, d, *J*=6.10 Hz), 3.85 (4 H, br. s.), 3.53 (3 H, s), 3.35 (2 H, ddd, *J*=15.95, 9.99, 6.10 Hz), 1.97 (1 H, br. s.), 1.48 (2 H, t, *J*=13.28 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.82 - 1.00 (2 H, m).

[00320] Cap-179 Enantiomer-2 was prepared similarly: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.50 (1 H, br. s.), 7.31 (1 H, br. s.), 3.84 (1 H, t, *J*=7.32 Hz), 3.53 (3 H, s), 3.29 - 3.41 (2 H, m), 1.99 (1 H, s), 1.48 (2 H, t, *J*=14.34 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.95 (1 H, q, *J*=12.21 Hz), 0.87 (1 H, q, *J*=11.80 Hz). [Note: the minor variation in the ^{1}H NMR profile of the enantiomers is likely a result of a difference in sample concentration.]

Cap-180 (racemic mixture)



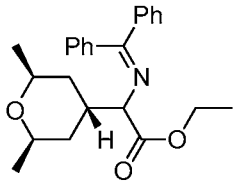
Cap-180, Step a



[00321] p-Tosyl-Cl (4.39 g, 23.0 mmol) was added to a solution of Cap-179, Step a (1.50 g, 11.5 mmol) and pyridine (3.73 mL, 46.1 mmol) in CH_2Cl_2 (50 mL) at room

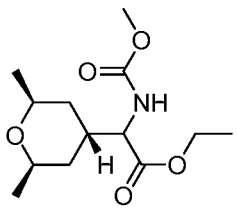
temperature and stirred for 2 days. The reaction was diluted with CH_2Cl_2, washed with water, then 1 N HCl. The organic layer was dried ($MgSO_4$) and concentrated to a yellow oil which was purified via BIOTAGE® (5% to 20% EtOAc/Hex; 40g column). A clear oil that solidified under vacuum and corresponding to Cap-180, Step a (2.89 g) was isolated. LC-MS: Anal. Calcd. for $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$: 591.21; found 591.3. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.24 Hz), 7.35 (2 H, d, *J*=7.93 Hz), 4.59 (1 H, tt, *J*=11.37, 4.96 Hz), 3.36 - 3.46 (2 H, m), 2.46 (3 H, s), 1.91 (2 H, dd, *J*=12.05, 5.04 Hz), 1.37 (2 H, dt, *J*=12.67, 11.52 Hz), 1.19 (6 H, d, *J*=6.10 Hz).

Cap-180, Step b



[00322] LiHMDS 1 N (7.09 mL, 7.09 mmol) was added to a solution of Cap-180, Step a (1.68 g, 5.91 mmol) and ethyl 2-(diphenylmethyleneamino)acetate (1.579 g, 5.91 mmol) in toluene (30 mL) at room temperature and the resulting mixture was then stirred for 16 h at 85 °C. The reaction was quenched with water (50 mL), extracted with EtOAc, washed with water, dried over $MgSO_4$, filtrated, and concentrated *in vacuo*. The residue was purified via BIOTAGE® (0% to 15% EtOAc/Hex; 40g column). A clear yellowish oil corresponding to Cap-180, Step b (racemic mixture; 0.64 g) was isolated. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{30}NO_3$: 380.22; found 380.03. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.70 (2 H, m), 7.45 - 7.51 (3 H, m), 7.38 - 7.44 (1 H, m), 7.31 - 7.37 (2 H, m), 7.13 - 7.19 (2 H, m), 4.39 (1 H, d, *J*=10.54 Hz), 4.16 - 4.26 (2 H, m), 3.29 - 3.39 (1 H, m), 2.93 - 3.03 (1 H, m), 2.70 (1 H, m, *J*=9.41, 4.14 Hz), 1.42 - 1.49 (2 H, m), 1.31 - 1.37 (1 H, m), 1.29 (4 H, t, *J*=7.15 Hz), 1.04 (6 H, dd, *J*=7.78, 6.27 Hz).

Cap-180, Step c

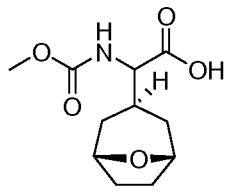


[00323] Cap-180, Step b (0.36 g, 0.949 mmol) was dissolved in THF (10 mL) and treated with 2 N HCl (1.897 mL, 3.79 mmol). The resulting clear solution was stirred at ambient temperature for 20 h and THF was removed under reduced pressure. The remaining aqueous layer was extracted with hexanes (3 X 20 mL) and after diluting with H_2O (20 mL), the aqueous phase was basified with 1 N NaOH to pH = 10 and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was taken up in CH_2Cl_2 (10.00 mL) and charged with DIEA (0.497 mL, 2.85 mmol) and methyl chloroformate (0.081 mL, 1.044 mmol). The resulting solution was stirred at ambient temperature for 2 h and the reaction mixture was quenched with water (10 mL) and the organic layer was removed under reduced pressure. Aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. An amber oil corresponding to Cap-180, Step c (0.21 g) was recovered and it was used without further purification. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{24}NO_5$: 273.17; found 274.06. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.20 (1 H, d, *J*=8.03 Hz), 4.59 (1 H, t, *J*=10.16 Hz), 4.11 - 4.27 (3 H, m), 3.69 - 3.82 (2 H, m), 3.64 (3 H, s), 1.95 - 2.07 (1 H, m), 1.63 (1 H, d, *J*=13.80 Hz), 1.41 (2 H, dd, *J*=8.03, 4.02 Hz), 1.31 - 1.37 (1 H, m), 1.26 (3 H, t, *J*=7.15 Hz), 1.16 (1 H, d, *J*=6.27 Hz), 1.12 (6 H, dd, *J*=6.15, 3.89 Hz).

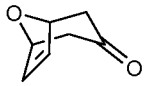
Cap-180 (racemic mixture)

[00324] Cap-180, Step c (0.32 g, 1.2 mmol) was dissolved in THF (10 mL) and charged with LiOH (0.056 g, 2.342 mmol) in water (3.33 mL) at 0 °C. The resulting solution was stirred at rt for 2 h. THF was removed under reduced pressure and the remaining residue was diluted with water (15 mL) and washed with Et_2O (2 x 10 mL). The aqueous layer was then acidified with 1N HCl to pH ~ 2 and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to yield Cap-180 (racemic mixture) (0.2 g) as a white foam. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{20}NO_5$: 246.13; found 246.00. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.14 (1 H, d, *J*=9.03 Hz), 4.65 (1 H, t, *J*=9.91 Hz), 3.63 - 3.89 (5 H, m), 1.99 - 2.13 (1 H, m), 1.56 - 1.73 (2 H, m), 1.48 - 1.55 (1 H, m), 1.35 - 1.48 (1 H, m), 1.27 (1 H, br. s.), 1.17 (6 H, d, *J*=6.02 Hz).

Cap-185 (Enantiomer-1 and Enantiomer-2)

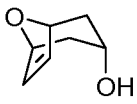


Cap-185, Step a



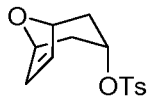
[00325] To a mixture of furan (1.075 mL, 14.69 mmol) and zinc (1.585 g, 24.24 mmol) in 1 mL of THF was added 1,1,3,3-tetrabromopropan-2-one (8.23 g, 22.03 mmol) and triethyl borate (5.25 mL, 30.8 mmol) in 4 mL of THF dropwise during 1 hour in dark. The resulting mixture was stirred at room temperature in dark for 17 hours. The resulting dark brown mixture was cooled to -15 °C, and 6 mL of water was added. The mixture was warmed to 0 °C and stirred at this temperature for 30 min. The mixture was then filtered and washed with ether. The filtrate was diluted with water and extracted with ether (3x). The combined organic layers were dried with $MgSO_4$ and concentrated to afford dark brown oil. The dark brown oil was dissolved in 6 mL of MeOH and the solution was added dropwise to a mixture of zinc (4.99 g, 76 mmol), copper (I) chloride (0.756 g, 7.64 mmol) and ammonium chloride (5.4 g, 101 mmol) in 20 mL of MeOH. The reaction temperature was maintained below 15 °C during addition. The mixture was then stirred at room temperature for 20 hours, filtered, and the filtrate was diluted with water and extracted with CH_2Cl_2 (3X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-14% EtOAc/Hex) to afford Cap-185, Step a as a white solid (1.0 g) as a white solid, which turned yellow soon. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.24 (2 H, s), 5.01 (2 H, d, *J*=4.88 Hz), 2.73 (2 H, dd, *J*=16.94, 5.04 Hz), 2.31 (2 H, d, *J*=16.79 Hz).

Cap-185, Step b



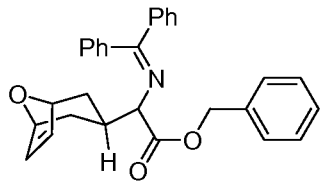
[00326] To a solution of Cap-185, Step a (240 mg, 1.933 mmol) in 2 mL of THF at -78 °C was added L-selectride (3.87 mL, 3.87 mmol) (1 M in THF) dropwise over 100 min. The resulting mixture was stirred at -78 °C for 1 hour and then at room temperature overnight. The mixture was then cooled to 0 °C, 4 mL of 20% NaOH aqueous solution was added, followed by 2 mL of H_2O_2 (30% water solution) dropwise. The resulting mixture was stirred for 1 hour and then neutralized with 6N HCl (~5 mL). The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (3X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-40% EtOAc/Hex) to afford Cap-185, Step b (180 mg) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.49 (2 H, s), 4.76 (2 H, d, *J*=4.27 Hz), 3.99 (1 H, t, *J*=5.77 Hz), 2.29 (2 H, ddd, *J*=15.18, 5.65, 4.02 Hz), 1.70 - 1.78 (2 H, m).

Cap-185, Step c



[00327] p-Tosyl-Cl (544 mg, 2.85 mmol) was added to a solution of Cap-185, Step b (180 mg, 1.427 mmol) and pyridine (0.462 mL, 5.71 mmol) in 5 mL of CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 2 days. The reaction was diluted with CH_2Cl_2 and washed with 1 N aq. HCl. The aqueous layer was extracted with CH_2Cl_2 (2X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-15% EtOAc/Hex) to afford Cap-185, Step c (210 mg) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.73 (2 H, d, *J*=8.24 Hz), 7.32 (2 H, d, *J*=8.24 Hz), 6.25 (2 H, s), 4.76 (1 H, t, *J*=5.65 Hz), 4.64 (2 H, d, *J*=3.66 Hz), 2.44 (3 H, s), 2.18 (2 H, td, *J*=10.07, 5.49 Hz), 1.71 (2 H, d, *J*=15.56 Hz).

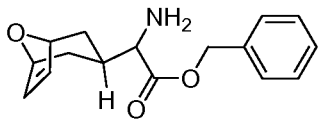
Cap-185, Step d



[00328] A microwave tube was charged with benzyl 2-(diphenylmethyleneamino)acetate (1.5 g, 4.57 mmol) and Cap-185, Step c (1.28 g, 4.57

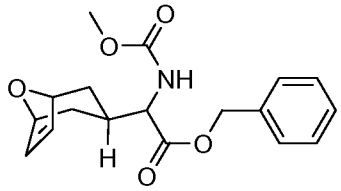
mmol) in 5 mL of toluene. The tube was sealed and LiHMDS (5.5 mL, 5.5 mmol) (1 N in toluene) was added dropwise under N_2. The resulting dark brown solution was heated at 100 °C in microwave for 5 hours. To the mixture was then added water and EtOAc. The layers were separated and the water phase was extracted with EtOAc (2X). The combined organic layers were concentrated to afford Cap-185, Step d as a racemic mixture of. The crude mixture was submitted to the next step without purification or separation. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{28}NO_3$ 438.21; found 438.4.

Cap-185, Step e



[00329] To a solution of the racemic mixture of Cap-185, Step d in 30 mL of THF was added HCl (20 mL) (2 N aq.). The resulting mixture was stirred at room temperature for 2 hours. After the reaction was done as judged by TLC, the two layers were separated. The aqueous layer was washed with EtOAc, neutralized with sat. $NaHCO_3$ aq. solution and then extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-185, Step e. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{20}NO_3$ 274.14; found 274.12.

Cap-185, Step f



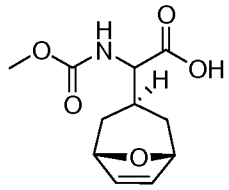
[00330] A solution of the crude Cap-185, Step e, DiPEA (1.24 mL, 7.1 mmol) and methyl chloroformate (0.55 mL, 7.1 mmol) in 5 mL of CH_2Cl_2 was stirred at room temperature for 1 hour. The mixture was then diluted with CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 0-40% EtOAc/Hex) to afford 700 mg of the racemic mixture. The mixture was then separated by chiral HPLC (CHIRALPAK® AD-H column, 30 x 250 mm, 5 um) eluting with 88% CO_2-12% EtOH at 70 mL/min to afford

240 mg of Enantiomer-1 and 310 mg of Enantiomer-2 of Cap-1, Step f as white solids. Enantiomer-1: LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; found 332.3. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.30 - 7.40 (5 H, m), 6.03 - 6.16 (2 H, m), 5.09 - 5.26 (3 H, m), 4.65 - 4.74 (2 H, m), 4.33 (1 H, dd, *J*=9.16, 4.88 Hz), 3.67 (3 H, s), 2.27 - 2.38 (1 H, m), 1.61 - 1.69 (1 H, m), 1.45 - 1.56 (1 H, m), 1.34 (1 H, dd, *J*=13.43, 5.19 Hz), 1.07 (1 H, dd, *J*=13.12, 5.19 Hz). Enantiomer-2: LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; found 332.06.

Cap-185 (Enantiomer-1 and Enantiomer-2)

[00331] To a hydrogenation bottle containing a solution Cap-185, Step f (Enantiomer-2) (300 mg, 0.905 mmol) in 10 mL of MeOH was added Pd/C (15 mg, 0.141 mmol) under a cover of nitrogen. The mixture was hydrogenated on a Parr shaker at 40 psi for 3 hours. The mixture was then filtered and the filtrate was concentrated to afford Cap-185 (Enantiomer-2) (200 mg) as a white solid. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{18}NO_5$ 244.12; found 244.2. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.33 (1 H, br. s.), 4.46 (2 H, d), 4.28 (1 H, br. s.), 3.68 (3 H, s), 2.35 (1 H, br. s.), 1.91 - 2.03 (2 H, m), 1.56 - 1.80 (4 H, m), 1.36 - 1.55 (2 H, m). [Note: Cap-185 (Enantiomer-1) can be obtained in a similar fashion.]

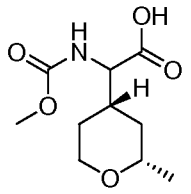
Cap-186



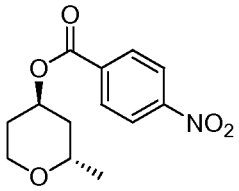
[00332] To a solution of the ester Cap-185, Step f (Enantiomer-2) (150 mg, 0.453 mmol) in 4 mL of MeOH was added NaOH (4 mL of 1 N in water, 4.00 mmol). The resulting mixture was stirred at room temperature for 3 hours. The methanol was then removed under vacuum, and the residue was neutralized with 1 N HCl solution and extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-186 that was contaminated with some benzyl alcohol (sticky white solid; 115 mg). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_5$ 242.10; found 242.1. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.10 - 6.19 (2 H, m), 5.36 (1 H, d, *J*=8.85 Hz), 4.75 -

4.84 (2 H, m), 4.28 (1 H, dd, *J*=8.55, 4.58 Hz), 3.68 (3 H, s), 2.33 - 2.45 (1 H, m), 1.60 - 1.72 (2 H, m), 1.30 - 1.48 (2 H, m).

Cap-187

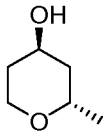


Cap-187, Step a



[00333] To a solution of Cap-178, Step e (2.2 g, 18.94 mmol), PPh_3 (24.84 g, 95 mmol) and 4-nitrobenzoic acid (14.24 g, 85 mmol) in 30 mL of benzene was added DEAD (42.9 mL, 95 mmol) dropwise. The resulting light orange solution was stirred at room temperature overnight. The solvent was then removed under vacuum and the residue was purified by flash chromatography (silica gel, 0-15% EtOAc/Hex) to afford Cap-187, Step a (2.3 g) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.27 - 8.34 (2 H, m), 8.20 - 8.26 (2 H, m), 5.45 (1 H, t, *J*=2.90 Hz), 3.83 - 3.96 (3 H, m), 1.90 - 2.03 (2 H, m), 1.80 - 1.88 (1 H, m), 1.61 - 1.70 (1 H, m), 1.21 (3 H, d, *J*=6.10 Hz).

Cap-187, Step b



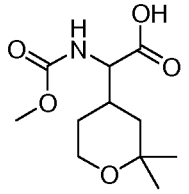
[00334] To a solution of Cap-187, Step a (2.3 g, 8.67 mmol) in 10 mL of MeOH was added sodium methoxide (2.372 mL, 8.67 mmol) (25% in Methanol). The resulting mixture was stirred at room temperature for 3 hours. Water was added, and the mixture was extracted with EtOAc (5X). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-

15% EtOAc/Hex, then 15-50% EtOAc/Hex) to afford Cap-187, Step b (0.85 g) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.19 - 4.23 (1 H, m), 3.82 - 3.91 (2 H, m), 3.73 - 3.79 (1 H, m), 1.79 - 1.88 (1 H, m), 1.62 - 1.68 (1 H, m), 1.46 - 1.58 (2 H, m), 1.14 (3 H, d, *J*=6.10 Hz).

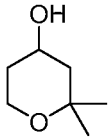
Cap-187

[00335] The individual enantiomers of Cap-187 were synthesized from Cap-187, Step b according to the procedure described for Cap-178. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; found 232.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.26 (1 H, d, *J*=7.78 Hz), 4.32 - 4.43 (1 H, m), 4.07 (1 H, dd, *J*=11.54, 3.51 Hz), 3.72 (3 H, s), 3.39 - 3.50 (2 H, m), 2.08 - 2.23 (1 H, m), 1.54 - 1.68 (1 H, m), 1.38 - 1.52 (1 H, m), 1.11 - 1.32 (5 H, m).

Cap-188 (four stereoisomers)

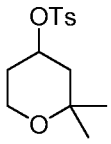


Cap-188, Step a



[00336] To a solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2 g, 15.60 mmol) in 50 mL of MeOH was slowly added sodium borohydride (0.649 g, 17.16 mmol). The resulting mixture was stirred at room temperature for 3 hours. To the mixture was then added 1 N HCl aqueous solution until it crosses into acidic pH range and then extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-188, Step a (1.9 g) as clear oil. The product was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.91 - 4.02 (1 H, m), 3.79 - 3.86 (1 H, m), 3.63 (1 H, td, *J*=12.05, 2.51 Hz), 1.82 - 1.93 (2 H, m), 1.40 - 1.53 (1 H, m), 1.29 - 1.38 (1 H, m), 1.27 (3 H, s), 1.20 (3 H, s).

Cap-188.1 and Cap-188.2, Step b

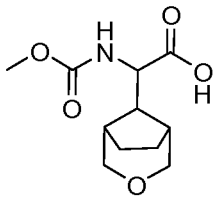


[00337] p-Tosyl-Cl (5.56 g, 29.2 mmol) was added to a solution of Cap-188, Step a (1.9 g, 14.59 mmol) and pyridine (4.72 mL, 58.4 mmol) in 100 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 3 days. To the reaction was added 10 mL of water, and the mixture was stirred at room temperature for an additional hour. The two layers were separated and the organic phase was washed with water and 1 N HCl aqueous solution. The organic phase was dried with $MgSO_4$ and concentrated to afford the mixture of two enantiomers as a light yellow solid. The mixture was then separated by chiral HPLC (CHIRALPAK® AD column, 21 x 250 mm, 10 um) eluting with 92% 0.1%diethylamine/Heptane-8% EtOH at 15 mL/min to afford Cap-188.1, Step b (1.0 g) and Cap-188.2, Step b (1.0 g). The absolute stereochemistry of the two enantiomers was not assigned. Cap-188.1, Step b: LC-MS: Anal. Calcd. for $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$ 591.21; found 591.3. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=8.24 Hz), 4.72 - 4.81 (1 H, m), 3.78 (1 H, dt, *J*=12.44, 4.16 Hz), 3.53 - 3.61 (1 H, m), 2.45 (3 H, s), 1.75 - 1.86 (2 H, m), 1.61 - 1.71 (1 H, m), 1.52 - 1.60 (1 H, m), 1.22 (3 H, s), 1.14 (3 H, s). Cap-188.2, Step b: LC-MS: Anal. Calcd. for $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$ 591.21; found 591.3;

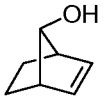
Cap-188

[00338] The four stereoisomers of Cap-188 could be synthesized from Cap-188.1, Step b and Cap-188.2, Step b, according to the procedure described for the preparation of Cap-178. Cap-188 (Steroisomer-1): LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{11}H_{19}NNaO_5$ 268.12; found 268.23. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.32 (1 H, d, *J*=8.55 Hz), 4.26 - 4.35 (1 H, m), 3.57 - 3.82 (5 H, m), 2.11 - 2.34 (1 H, m), 1.25 - 1.58 (4 H, m), 1.21 (6 H, d, *J*=6.10 Hz). Cap-188 (Stereoisomer-2): LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{20}NO_5$ 246.13; found 246.1. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.25 (1 H, d, *J*=8.55 Hz), 4.33 (1 H, dd, *J*=8.39, 5.04 Hz), 3.80 (1 H, dd, *J*=11.90, 3.97 Hz), 3.62 - 3.76 (4 H, m), 2.20 - 2.32 (1 H, m), 1.52 - 1.63 (1 H, m), 1.27 - 1.49 (3 H, m), 1.22 (6 H, d, *J*=14.04 Hz).

Cap-189

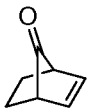


Cap-189, Step a



[00339] To a solution of phenylmagnesium bromide (113 mL, 340 mmol) (3 M in ether) in 100 mL of ether was added dropwise exo-2,3-epoxynorbornane (25 g, 227 mmol) in 50 mL of ether. After the initial exotherm, the mixture was heated to reflux overnight. The reaction was then cooled to room temperature and quenched carefully with water (~ 10 mL). The mixture was diluted with ether and washed with a 3 N HCl aqueous solution (~ 160 mL). The aqueous layer was extracted with ether (2X) and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-18% EtOAc/Hex) to afford Cap-189, Step a (11 g). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.03 - 6.11 (2 H, m), 3.76 (1 H, d, *J*=11.29 Hz), 2.72 - 2.81 (2 H, m), 1.98 (1 H, d, *J*=11.29 Hz), 1.67 - 1.76 (2 H, m), 0.90 - 0.97 (2 H, m).

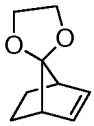
Cap-189, Step b



[00340] To a solution of oxalyl chloride (59.9 mL, 120 mmol) in 200 mL of CH_2Cl_2 at -78 °C was added DMSO (17.01 mL, 240 mmol) in 100 mL of CH_2Cl_2. The mixture was stirred for 10 min, and Cap-189, Step a (11 g, 100 mmol) in 150 mL of CH_2Cl_2 was added followed by Et_3N (72.4 mL, 519 mmol) in 30 mL of CH_2Cl_2. The mixture was stirred at -78 °C for 30 min and then warmed to room temperature. Water (150 mL) was added and the mixture was stirred at room temperature for 30 mins. The two layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (2X). The organic layers

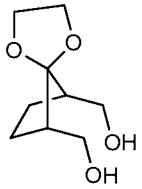
were combined, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-5% EtOAc/Hex) to afford Cap-189, Step b (5.3 g) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.50 - 6.55 (2 H, m), 2.78 - 2.84 (2 H, m), 1.92 - 1.99 (2 H, m), 1.17 - 1.23 (2 H, m).

Cap-189, Step c



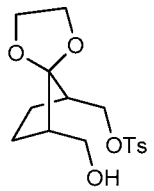
[00341] A mixture of Cap-189, Step b (5.3 g, 49.0 mmol), *p*-toluenesulfonic acid monohydrate (1.492 g, 7.84 mmol) and ethylene glycol (4.10 mL, 73.5 mmol) in 100 mL of benzene was refluxed for 4 hours and then stirred at room temperature overnight. The reaction was partitioned between Et_2O and aqueous sat. $NaHCO_3$ solution and the two layers were separated. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-6% EtOAc/Hex) to afford Cap-189, Step c (5.2 g) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.20 (2 H, t, *J*=2.13 Hz), 3.90 - 3.97 (2 H, m), 3.81 - 3.89 (2 H, m), 2.54 (2 H, m), 1.89 - 1.99 (2 H, m), 0.95 - 1.03 (2 H, m).

Cap-189, Step d



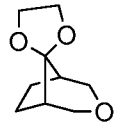
[00342] A solution of Cap-189, Step c (5.2 g, 34.2 mmol) in 60 mL of MeOH and 50 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone gas until a light blue color was apparent. The reaction was then bubbled with N_2 to remove the excess ozone gas (blue color disappeared) and sodium borohydride (1.939 g, 51.3 mmol) was added into the reaction. The reaction was then warmed to 0 °C. Acetone was added into the mixture to quench the excess sodium borohydride. The mixture was concentrated and the residue was purified by flash chromatography (silica gel, 100% EtOAc) to afford Cap-189, Step d (5.0 g) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.99 - 4.09 (4 H, m), 3.68 (4 H, m), 2.17 - 2.29 (2 H, m), 1.92 - 2.10 (2 H, m), 1.77 - 1.88 (2 H, m), 1.57 - 1.70 (2 H, m).

Cap-189, Step e



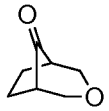
[00343] To a solution of Cap-189, Step d (1 g, 5.31 mmol) in 20 mL of CH_2Cl_2 was added silver oxide (3.8 g), p-Ts-Cl (1.215 g, 6.38 mmol) and KI (0.176 g, 1.063 mmol). The resulting solution was stirred at room temperature for 3 days. The mixture was then filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, 60% EtOAc/Hex) to afford Cap-189, Step e (0.79 g) as clear oil. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{16}H_{22}NaO_6S$ 365.10; found 365.22. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.36 (2 H, d, *J*=8.03 Hz), 4.11 - 4.17 (1 H, m), 3.85 - 4.06 (5 H, m), 3.64 - 3.71 (1 H, m), 3.55 - 3.63 (1 H, m), 2.47 (3 H, s), 2.32 - 2.43 (1 H, m), 2.15 - 2.27 (1 H, m), 1.70 - 1.89 (2 H, m), 1.52 - 1.66 (1 H, m), 1.35 - 1.47 (1 H, m).

Cap-189, Step f



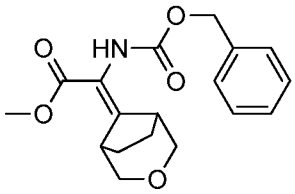
[00344] To a solution of Cap-189, Step e (2.2 g, 6.43 mmol) in 40 mL of MeOH was added potassium carbonate (1.776 g, 12.85 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was then diluted with water and EtOAc. The two layers were separated. The aqueous layer was extracted with EtOAc (2X). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-15% EtOAc/Hex) to afford Cap-189, Step f (0.89 g, 5.23 mmol, 81%) as clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.89 - 4.02 (6 H, m), 3.58 (2 H, dd, *J*=10.79, 2.51 Hz), 1.69 - 1.89 (6 H, m).

Cap-189, Step g



[00345] To the solution of Cap-189, Step f (890 mg, 5.23 mmol) in 15 mL of THF was added HCl (15 mL, 45.0 mmol) (3 M aqueous). The resulting mixture was stirred at room temperature overnight. The mixture was then diluted with ether and the two layers were separated. The aqueous phase was extracted with ether (2X) and the combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-189, Step g (0.95 g, containing some residual solvents). The product was used in the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.95 - 4.00 (2 H, m), 3.85 (2 H, d, *J*=10.68 Hz), 2.21 - 2.28 (2 H, m), 1.99 - 2.04 (2 H, m), 1.90 - 1.96 (2 H, m).

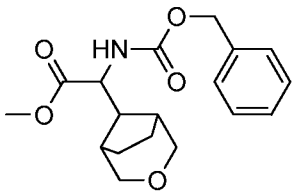
Cap-189, Step h (Enantiomer-1 and Enantiomer-2)



[00346] To a solution of (+/-)-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (1733 mg, 5.23 mmol) in 6 mL of THF at -20 °C was added 1,1,3,3-tetramethylguanidine (0.723 mL, 5.75 mmol). The resultant light yellow mixture was stirred at -20 °C for 1 hour, and Cap-189, Step g (660 mg, 5.23 mmol) in 3 mL of THF was added and mixture was then stirred at room temperature for 3 days. The reaction mixture was then diluted with EtOAc, washed with a 0.1 N HCl aq. solution. The aqueous layer was extracted with EtOAc (2X) and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 0-4% EtOAc/CH_2Cl_2) to afford 960 mg of the racemic mixture. The mixture was separated by chiral HPLC (CHIRALPAK® AD column, 21 x 250 mm, 10 um) eluting with 90% 0.1% diethylamine/Heptane-10% EtOH at 15 mL/min to afford Cap-189, Step h (Enantiomer-1; 300 mg) and Cap-189, Step h (Enantiomer-2; 310 mg) as white solids. Cap-189, Step h (Enantiomer-1): LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; found 332.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.29 - 7.41 (5 H, m), 6.00 (1 H, br. s.), 5.13 (2 H, s), 3.63 - 3.87 (8 H, m), 2.84 (1 H, br. s.), 1.84 - 2.02 (2 H, m), 1.63 - 1.84 (2 H, m). Cap-189,

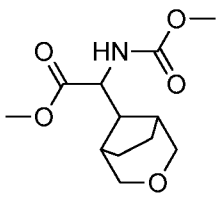
Step h (Enantiomer-2): LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; found 332.2.

Cap-189, Step i



[00347] N_2 was bubbled through a solution of Cap-189, Step h (Enantiomer-2; 290 mg, 0.875 mmol) in 10 mL of MeOH in a 500 mL hydrogenation bottle for 30 mins. To the solution was added (S,S)-Me-BPE-Rh (9.74 mg, 0.018 mmol), and the mixture was then hydrogenated at 60 psi for 6 days. The mixture was concentrated, and chiral analytical HPLC (CHIRALPAK® OJ column) indicated that there were a small amount of remaining starting material and one major product. The residue was then separated by chiral HPLC (CHIRALPAK® OJ column, 21 x 250 mm, 10 um) eluting with 70% 0.1%diethylamine/ Heptane-30% EtOH at 15 mL/min to afford Cap-189, Step i, (150 mg) as clear oil. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{24}NO_5$ 334.17; found 334.39. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.28 - 7.41 (5 H, m), 5.12 - 5.18 (1 H, m), 5.09 (2 H, s), 4.05 (1 H, t, *J*=10.07 Hz), 3.75 (3 H, s), 3.60 - 3.72 (2 H, m), 3.41 - 3.50 (2 H, m), 2.10 (1 H, br. s.), 1.72 - 1.99 (6 H, m).

Cap-189, Step j



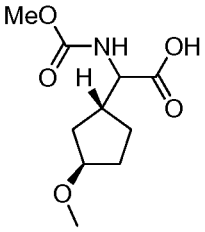
[00348] To a solution of Cap-189, Step i (150 mg, 0.450 mmol) in 10 mL of MeOH in a hydrogenation bottle were added dimethyl dicarbonate (0.072 mL, 0.675 mmol) and 10% Pd/C (23.94 mg, 0.022 mmol) under a cover of nitrogen cover. The mixture was then hydrogenated on Parr-shaker at 45 psi overnight. The mixture was filtered and the filtrate was concentrated to afford Cap-189, Step j (110 mg) as a clear oil. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}NO_5$ 258.13; found 258.19. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.08 (1

H, d, *J*=9.16 Hz), 4.03 (1 H, t, *J*=10.07 Hz), 3.75 (3 H, s), 3.60 - 3.72 (5 H, m), 3.46 (2 H, t, *J*=10.38 Hz), 2.11 (1 H, br. s.), 1.72 - 1.99 (6 H, m).

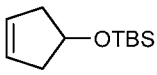
Cap-189

[00349] To a mixture of Cap-189, Step j (110 mg, 0.428 mmol) in 2 mL of THF and 1 mL of water was added LiOH (0.641 mL, 1.283 mmol) (2 N aq.). The resulting mixture was stirred at room temperature overnight. The mixture was neutralized with a 1 N HCl aq. solution and extracted with EtOAc (3X). The combined organic layers were dried with $MgSO_4$ and concentrated to afford Cap-189 (100 mg) as a white solid. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{11}H_{17}NNaO_5$ 266.10; found 266.21. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.10 (1 H, d, *J*=9.16 Hz), 4.02 (1 H, t, *J*=10.07 Hz), 3.62 - 3.78 (5 H, m), 3.49 (2 H, d, *J*=10.68 Hz), 2.07 - 2.22 (2 H, m), 1.72 - 1.98 (6 H, m).

Cap-190 (diastereomeric mixture)

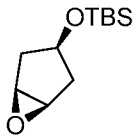


Cap-190, Step a



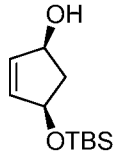
[00350] To a mixture of cyclopent-3-enol (2.93 g, 34.8 mmol) and imidazole (5.22 g, 77 mmol) in 30 mL of DMF at 0 °C was added *t*-butyldimethylchlorosilane (6.30 g, 41.8 mmol). The resulting colorless mixture was stirred at room temperature overnight. Hexanes and water were then added to the mixture and the two layers were separated. The aqueous layer was extracted with EtOAc (2X) and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 2% EtOAc/Hex) to afford Cap-190, Step a (6.3 g) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.65 (2 H, s), 4.49 - 4.56 (1 H, m), 2.56 (2 H, dd, *J*=15.26, 7.02 Hz), 2.27 (2 H, dd, *J*=15.26, 3.36 Hz), 0.88 (9 H, s), 0.06 (6 H, s).

Cap-190, Step b



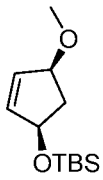
[00351] To a solution of Cap-190, Step a (2.3 g, 11.59 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added m-CPBA (5.60 g, 16.23 mmol) in 5 portions. The reaction mixture was stirred at room temperature overnight. Hexanes and water were then added to the mixture and the two layers were separated. The organic layer was washed with 50 mL aq. 10% $NaHSO_3$ and brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 3%-6% EtOAc/Hex) to afford Cap-190, Step b (1.42 g) and its trans diastereomer (0.53 g) as clear oils. Cap-190, Step b (*cis*): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.39 - 4.47 (1 H, m), 3.47 (2 H, s), 2.01 - 2.10 (2 H, m), 1.93 - 2.00 (2 H, m), 0.88 (9 H, s), 0.04 (6 H, s). Cap-190, Step b (*trans*): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.04 - 4.14 (1 H, m), 3.47 (2 H, s), 2.41 (2 H, dd, *J*=14.05, 7.28 Hz), 1.61 (2 H, dd, *J*=14.18, 6.90 Hz), 0.87 (9 H, s), 0.03 (6 H, s).

Cap-190, Step c



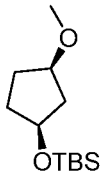
[00352] To a solution of (S)-1,2′-methylenedipyrrolidine (0.831 g, 5.39 mmol) in 15 mL of benzene at 0 °C was added dropwise *n*-butyllithium (4.90 mL, 4.90 mmol) (1 M in hexane). The solution turned bright yellow. The mixture was stirred at 0 °C for 30 min. Cap-190, Step b (cis-isomer; 0.7 g, 3.27 mmol) in 10 mL of benzene was then added and the resulting mixture was stirred at 0 °C for 3 hours. EtOAc and sat. NH_4Cl aq. solution were added into the mixture, and the two layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/Hex) to afford Cap-190, Step c (400 mg) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.84 - 5.98 (2 H, m), 4.53 - 4.69 (2 H, m), 2.63 - 2.73 (1 H, m), 1.51 (1 H, dt, *J*=13.73, 4.43 Hz), 0.89 (9 H, s), 0.08 (6 H, s).

Cap-190, Step d



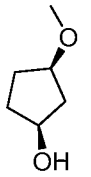
[00353] To a solution of Cap-190, Step c (400 mg, 1.866 mmol), MeI (1.866 mL, 3.73 mmol) (2 M in *t*-butyl methyl ether) in 5 mL of THF at 0 °C was added NaH (112 mg, 2.80 mmol) (60% in mineral oil). The resulting mixture was allowed to warm up to room temperature and stirred at room temperature overnight. The reaction was then quenched with water and extracted with EtOAc (3X). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (silica gel, 5% EtOAc/Hex) to afford Cap-190, Step d (370 mg) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.92 - 5.96 (1 H, m), 5.87 - 5.91 (1 H, m), 4.64 - 4.69 (1 H, m), 4.23 - 4.28 (1 H, m), 3.32 (3 H, s), 2.62 - 2.69 (1 H, m), 1.54 (1 H, dt, *J*=13.12, 5.49 Hz), 0.89 (9 H, s), 0.07 (5 H, d, *J*=1.83 Hz).

Cap-190, Step e



[00354] To a solution of Cap-190, Step d (400 mg, 1.751 mmol) in 10 mL of EtOAc in a hydrogenation bottle was added platinum(IV) oxide (50 mg, 0.220 mmol). The resulting mixture was hydrogenated at 50 psi on Parr shaker for 2 hours. The mixture was then filtered through CELITE®, and the filtrate was concentrated to afford Cap-190, Step e (400 mg) as a clear oil. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{27}O_2Si$ 231.18; found 231.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.10 - 4.17 (1 H, m), 3.65 - 3.74 (1 H, m), 3.27 (3 H, s), 1.43 - 1.80 (6 H, m), 0.90 (9 H, s), 0.09 (6 H, s).

Cap-190, Step f

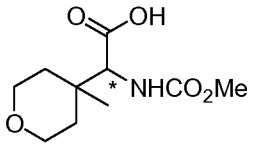


[00355] To a solution of Cap-190, Step e (400 mg, 1.736 mmol) in 5 mL of THF was added TBAF (3.65 mL, 3.65 mmol) (1 N in THF). The color of the mixture turned brown after several min., and it was stirred at room temperature overnight. The volatile component was removed under vacuum, and the residue was purified by flash chromatography (silica gel, 0-25% EtOAc/Hex) to afford Cap-190, Step f (105 mg) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.25 (1 H, br. s.), 3.84 - 3.92 (1 H, m), 3.29 (3 H, s), 1.67 - 2.02 (6 H, m).

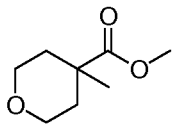
Cap-190

[00356] Cap-190 was then synthesized from Cap-190, Step f according to the procedure described for Cap-182. LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{10}H_{17}NNaO_5$ 254.10; found 254.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.25 (1 H, d, *J*=8.55 Hz), 4.27 - 4.41 (1 H, m), 3.81 - 3.90 (1 H, m), 3.69 (3 H, s), 3.26 (3 H, s), 2.46 - 2.58 (1 H, m), 1.76 - 1.99 (3 H, m), 1.64 - 1.73 (1 H, m), 1.40 - 1.58 (1 H, m), 1.22 - 1.38 (1 H, m).

Cap-191 (Enantiomer-1)



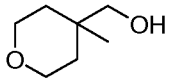
Cap-191, Step a



[00357] To a solution of diisopropylamine (3 ml, 21.05 mmol) in THF (3 ml) at -78 °C under nitrogen was added n-butyl lithium (2.5 M in hexanes; 8.5 ml, 21.25 mmol). The reaction was stirred at -78 °C for 10 min then brought up to 0 °C for 25 min. The reaction was cooled down again to -78 °C, methyl tetrahydro-2H-pyran-4-carboxylate (3 g, 20.81 mmol) in THF (3 ml) was added. The reaction was stirred at -78 °C for 15 min

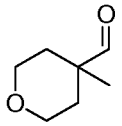
then brought up to 0 °C for 30 min. The reaction was cooled down to -78 °C, methyl iodide (1.301 ml, 20.81 mmol) was added. After the addition, the cold bath was removed and the reaction was allowed to slowly warm up to ~25 °C and stirred for 22h. Ethyl acetate and aqueous HCl (0.1N) were added, and the organic layer was separated and washed with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was loaded on a Thomson's silica gel cartridge eluting with 10% ethyl acetate/hexanes to afford a light yellow oil (2.83 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.73-3.66 (m, 2H), 3.66 (s, 3H), 3.40-3.30 (m, 2H), 1.95-1.93 (dm, 1H), 1.92-1.90 (dm, 1H), 1.43 (ddd, J = 13.74, 9.72, 3.89, 2H), 1.18 (s, 3H).

Cap-191, Step b



[00358] To a solution of Cap-191, Step a (3 g, 18.96 mmol) in toluene (190 ml) at -78 °C under nitrogen was added diisobutylaluminum hydride (1.5M in toluene; 26.5 ml, 39.8 mmol) dropwise. The reaction was continued to stir at -78 °C for 1.5h., and the bath was removed and was stirred for 18h. The reaction was quenched with MeOH (20 mL). HCl (1M, 150 mL) was added and the mixture was extracted with EtOAc (4 x 40 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified with flash chromatography (silica gel; 40% ethyl acetate/hexanes) to afford a colorless oil (1.36 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.77 (dt, J = 11.73, 4.55, 2H), 3.69-3.60 (m, 2H), 3.42 (s, 2H), 1.71-1.40 (bs, 1H)1.59 (ddd, J = 13.74, 9.72, 4.39, 2H), 1.35-1.31 (m, 1H), 1.31-1.27 (m, 1H), 1.06 (s, 3H).

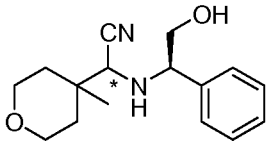
Cap-191, Step c



[00359] To a solution of DMSO (5.9 ml, 83 mmol) in CH_2Cl_2 (85 ml) at -78 °C under nitrogen was added oxalyl chloride (3.8 ml, 43.4 mmol) and stirred for 40 min. A solution of Cap-191, Step b (4.25 g, 32.6 mmol) in CH_2Cl_2 (42.5 ml) was then added.

The reaction was continued to be stirred at -78 °C under nitrogen for 2h. The reaction was quenched with cold 20% K_2HPO_4 (aq) (10 mL) and water. The mixture was stirred at ~25 °C for 15 min, diluted with diethyl ether (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (4 mL) and purified with flash chromatography (silica gel, eluting with CH_2Cl_2) to afford a colorless oil (2.1 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.49 (s. 1H), 3.80 (dt, J = 11.98,4.67, 2H), 3.53 (ddd, J = 12.05, 9.41, 2.89, 2H), 1.98 (ddd, J = 4.71, 3.20, 1.38, 1H), 1.94 (ddd, J= 4.71, 3.20, 1.38, 1H), 1.53 (ddd, J = 13.87, 9.60, 4.14, 2H), 1.12 (s, 3H).

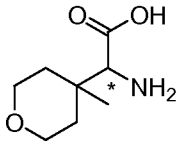
Cap-191, Step d



[00360] To a solution of Cap-191c (2.5 g, 19.51 mmol) in $CHCl_3$ (20 ml) under nitrogen at ~25 °C was added (*R*)-2-amino-2-phenylethanol (2.94 g, 21.46 mmol) and stirred for 5h. The reaction was cooled to 0 °C, trimethylsilyl cyanide (3.8 ml, 30.4 mmol) was added dropwise. The cold bath was removed and the reaction was allowed to stir at ~25 °C under nitrogen for 15.5 h. The reaction was treated with 3N HCl (20 mL) and water (20 mL), and the product was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried ($NaSO_4$), filtered, and concentrated *in vacuo*. The residue was purified with flash chromatography (silica gel; 40% ethyl acetate/hexanes) to afford two diastereomers: Cap-191, Step d1 (diastereomer 1) as a colorless oil which solidified into a white solid upon standing (3 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.42-7.26 (m, 5H), 5.21 (t, J = 5.77, 1H), 3.87 (dd, J = 8.53, 4.52, 1H), 3.61-3.53 (m, 1H), 3.53-3.37 (m, 5H), 3.10 (d, J = 13.05, 1H), 2.65 (d, J = 13.05, 1H), 1.64-1.55 (m, 1H), 1.55-1.46 (m,1H), 1.46-1.39 (m, 1H), 1.31-1.23 (m, 1H), 1.11 (s, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{23}N_2O_2$: 275.18; found 275.20. Cap-191, Step d2 (diastereomer 2) as a light yellow oil (0.5 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.44-7.21 (m, 5H), 4.82 (t, J = 5.40, 1H), 3.82-3.73 (m, 1H), 3.73-3.61 (m, 3H), 3.61-3.37 (m, 5H), 2.71 (dd,

J = 9.29, 4.77, 1H), 1.72-1.55 (m, 2H), 1.48-1.37 (m, 1H), 1.35-1.25 (m, 1H), 1.10 (s, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{23}N_2O_2$: 275.18; found 275.20.

Cap-191, Step e



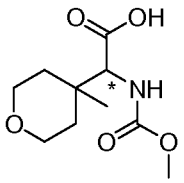
[00361] To a solution of Cap-191, Step d2 (diastereomer 2) (0.4472 g, 1.630 mmol) in CH_2Cl_2 (11 ml) and MeOH (5.50 ml) at 0 °C under nitrogen was added lead tetraacetate (1.445 g, 3.26 mmol). The reaction was stirred for 1.5h, the cold bath was removed and stirring was continued for 20h. The reaction was treated with a phosphate buffer (pH = 7; 6 mL) and stirred for 45 min. The reaction was filtered over CELITE®, washed with CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 25 mL), and the combined organic layers was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified with flash chromatography (silica gel; 15% ethyl acetate/hexanes) to afford the imine intermediate as a colorless oil (181.2 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.55 (d, J = 1.00, 1H), 7.89-7.81 (m, 2H), 7.61-7.46 (m, 3H), 4.80 (d, J = 1.00, 1H), 3.74 (tt, J = 11.80, 4.02, 2H), 3.62-3.46 (m, 2H), 1.79-1.62 (m, 2H), 1.46-1.30 (m, 2H), 1.15 (s, 3H).

[00362] The imine intermediate was taken up in 6N HCl (10 mL) and heated at 90 °C for 10 days. The reaction was removed from the heat, allowed to cool to room temperature and extracted with ethyl acetate (3 x 25 mL). The aqueous layer was concentrated in *vacuo* to afford an off-white solid. The solid was taken up in MeOH and loaded on a pre-conditioned MCX (6 g) cartridge, washed with MeOH followed by elution with 2N NH_3/MeOH solution and concentrated *in vacuo* to afford an off-white solid (79.8 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.33-13.51 (bs, 1H), 8.30 (bs, 3H), 3.82-3.75 (m, 1H), 3.70 (dt, J = 11.80, 4.02, 2H), 3.58-3.43 (m, 2H), 1.76-1.60 (m, 2H), 1.47-1.36 (m, 1H), 1.36-1.27 (m, 1H), 1.08 (s, 3H). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{16}NO_3$: 174.11; found 174.19.

Cap-191 (Enantiomer-1)

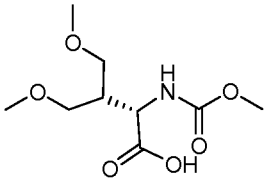
[00363] To a solution of Cap-191, Step e (0.0669 g, 0.386 mmol) and sodium carbonate (0.020 g, 0.193 mmol) in sodium hydroxide (1M aq.; 0.4 ml, 0.40 mmol) at 0 °C was added methyl chloroformate (0.035 ml, 0.453 mmol) dropwise. The reaction was removed from the cold bath and allowed to stir at ~25 °C for 3h. The reaction was washed with diethyl ether (3 x 20 mL). The aqueous layer was acidified with 12 N HCl (pH ~ 1-2), and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford Cap-191 as a colorless film (66.8 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.10-12.37 (bs, 1H), 7.37 (d, J = 9.04, 1H), 4.02 (d, J = 9.29, 1H), 3.72-3.57 (m, 2H), 3.56 (s, 3H), 3.54-3.44 (m, 2H), 1.65 (ddd, J = 13.61, 9.72, 4.27, 1H), 1.53 (ddd, J = 13.68, 9.66, 4.27, 1H), 1.41-1.31 (m, 1H), 1.31-1.22 (m, 1H), 1.00 (s, 3H). LC-MS: Anal. Calcd. for $[M+Na]^+$ $C_{10}H_{17}NO_5Na$: 254.10; found 254.11.

Cap-192 (Enantiomer-2)

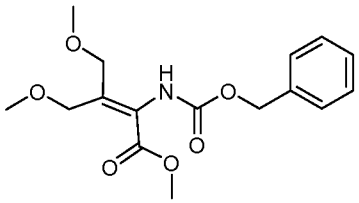


[00364] Cap-192 (Enantiomer-2) was prepared from Cap-191, Step d1 according to the procedure described for the preparation of its enantiomer Cap-191.

Cap-193

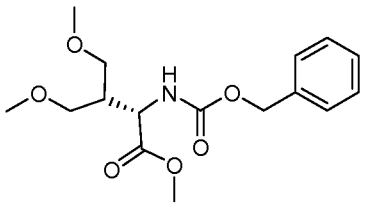


Cap-193, Step a



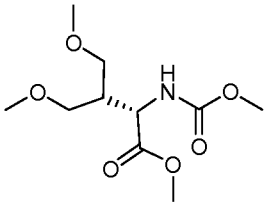
[00365] To a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (1.45 g, 4.2 mmol) in DCM was added DBU (0.70 ml, 4.7 mmol). The reaction mixture was stirred for 10 min, followed by addition of a solution of 1,3-dimethoxypropan-2-one (0.5 g, 4.2 mmol) in DCM. The reaction mixture was stirred at room temperature for 18 hrs. The reaction mixture was charged to an 80 g silica gel cartridge which was eluted with an 18 min gradient of 0-70% EtOAc in hexane to afford Cap-193, Step a (0.8 g) as a thick oil. ^{1}H NMR (400 MHz, MeOD) ppm 7.23 - 7.43 (5 H, m), 4.99 - 5.18 (2 H, m), 4.16 (2 H, s), 4.06 (2 H, s), 3.66 - 3.78 (3 H, s), 3.26 (3 H, s), 3.23 (3 H, s). LC-MS: Anal. Calcd. For $[M+Na]^+$ $C_{16}H_{21}NNaO_6$: 346.14; found: 346.12.

Cap-193, Step b



[00366] A reaction mixture of ester Cap-193, Step a (0.5 g) and (+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate (0.1 g) in MeOH was stirred under 55 psi of H_2 for 18 hrs. The reaction mixture was concentrated to dryness. The residue was charged to a 25 g silica gel cartridge and eluted with an 18 min gradient of 0-80% EtOAc in hexane to afford Cap-193, Step b (0.49 g) as a clear oil. LC-MS: Anal. Calcd. For $[M+Na]^+$ $C_{16}H_{23}NNaO_6$: 348.15; found: 348.19.

Cap-193, Step c

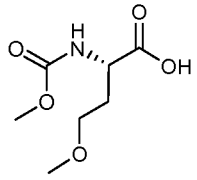


[00367] A reaction mixture of Cap-193, Step b (0.16 g), dimethyl dicarbonate (0.13 g) and 10% Pd/C (0.026 g) in EtOAc was stirred under H_2 at room temperature for 2 hrs. The reaction mixture was filtered and concentrated to yield the methyl carbamate Cap-193, Step c. LC-MS: Anal. Calcd. For $[M+Na]^+$ $C_{10}H_{19}NNaO_6$: 272.12; found: 272.07.

Cap-193

[00368] To a solution of ester Cap-193, Step c in THF (1 mL) and MeOH (0.25 mL) was added 1 N NaOH (1 mL). The reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated and diluted with EtOAc and 1 N HCl. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with sat. NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated to yield Cap-193 (0.082 g). ^{1}H NMR (400 MHz, $CDCl_3$) 5.99 (1 H, d, *J*=8.56 Hz), 4.57 (1 H, dd, *J*=8.56, 3.27 Hz), 3.67 (3 H, s), 3.49 (2 H, d, *J*=4.28 Hz), 3.45 - 3.44 (2 H, m), 3.26 - 3.35 (6 H, m). LC-MS: Anal. Calcd. For $[M+Na]^+$ $C_9H_{17}NNaO_6$: 258.11; found: 258.13.

Cap-194



[00369] Piperidine (1.0 mL, 10 mmol) was added to a solution of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-4-methoxybutanoic acid (0.355 g, 1 mmol) in DMF (3 mL), and the mixture was stirred at rt for 3 h. The volatiles were removed and the residue was partitioned between sat. $NaHCO_3$ (aq.) (5 mL) and EtOAc (5 mL). The aqueous layer was further washed with EtOAc and Et_2O. To the aqueous solution was added Na_2CO_3 (212 mg, 2.0 mmol) followed by methyl chloroformate (0.16 mL, 2.0 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was acidified with 1 N HCl (aq.) until pH <7 and then extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash silica chromatography (EtOAc/hexanes, gradient from 20% to 70%) to yield (S)-4-methoxy-2-(methoxycarbonylamino)butanoic acid (Cap-194) (91.5 mg) as viscous colorless oil. LC-MS retention time = 0.61 min; m/z 214 $[M+Na]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water :90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, chloroform-d) δ ppm 7.41 (br. s., 1 H), 5.74 - 6.02 (m, 1 H), 4.32 - 4.56 (m, 1 H), 3.70 (s, 3 H), 3.54 (t, *J*=5.0 Hz, 2 H), 3.34 (s, 3 H), 1.99 - 2.23 (m, 2 H).

Example Section

[00370] Low resolution mass analysis was conducted on a Shimadzu LC system coupled with Waters MICROMASS® ZQ MS system (Cond. 1) or Waters Acquity HPLC with Waters PDA UV-Vis detection and Waters ZQ MS (Cond. 2). Retention time (R_t) were derived by employing the following conditions, and it should be noted that retention times may vary slightly between instruments:

Condition 1a

Column = PHENOMENEX® Luna 4.6X 30 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 1b

Column = Waters Acquity BEH C18; 1.7 μm; 150 X 2.1 mm ID; (at 35C)
Hold 10%B = 0-1min
10-50%B = 0-25 min
50-98%B = 25-33 min
Hold 98%B = 32-35 min
98-10%B = 35.0-35.5 min
Hold 10%B = 35.5-40 min
Flow rate = 0.35 ml/min
Wavelength = 254 nm
Solvent A = 0.05% TFA in water
Solvent B = 0.05% TFA in CH_3CN

Condition 1c

Column = Waters Acquity BEH C18; 1.7 μm; 150 X 2.1 mm ID; (at 35 °C)

Hold 10%B = 0-1min

10-60%B = 1-4 min

60-98%B = 4-21 min

Hold 98%B = 21-21.5 min

98-10%B = 21.5-22 min

Hold 10%B = 22-25 min

Flow rate = 0.35 ml/min

Wavelength = 315 nm

Solvent A = 0.05% TFA in water

Solvent B = 0.05% TFA in CH_3CN

Condition 2a

Column = Waters SunFire C18, 4.6X150 mm, 3.5 μm

Start %B = 10

Final %B = 50

Gradient time = 20 min

Stop time = varies 25 to 40 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Solvent A = 0.1% TFA in 5% CH_3CN/95%H_2O

Solvent B = 0.1% TFA in 95% CH_3CN/5% H_2O

Condition 2b

Column = Waters Xbridge phenyl, 4.6X150 mm, 3 μm

Start %B = 10

Final %B = 50

Gradient time = 20 min

Stop time = varies 25 to 40 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Solvent A = 0.1% TFA in 5% CH_3CN/95%H_2O

Solvent B = 0.1% TFA in 95% CH_3CN/5% H_2O

Condition 3

Column = PHENOMENEX® Luna C18 (2), 3 u, 150x4.6mm

Start %B = 0

Final %B = 100

Gradient time: = 10 min

Flow rate = 1 mL/min

Wavelength = 220 and 256 nm

Solvent A = H_2O/CH_3CN (95:5) + 0.05% TFA

Solvent B = H_2O/CH_3CN (5:95) + 0.05% TFA

Condition OL1

Column = PHENOMENEX® Luna 3.0 X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition OL2

Column = PHENOMENEX® Luna 50X 2 mm 3 u

Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 0.8 mL/min

Oven Temp = 40 °C

Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% Acetonitrile/90%H_2O
Solvent B = 0.1% TFA in 90% Acetonitrile/10% H_2O

Condition OL3
Column = Waters Acquity BEH C18; 1.7 μm; 150 X 2.1 mm ID; (at 35 °C)
Hold 10%B = 0-1min
10-60%B = 1-4 min
60-98%B = 4-21 min
Hold 98%B = 21-21.5 min
98-10%B = 21.5-22 min
Hold 10%B = 22-25 min
Flow rate = 0.35 ml/min
Wavelength = 315 nm
Solvent A = 0.05% TFA in water
Solvent B = 0.05% TFA in CH_3CN

Condition OL4a
Column = Waters SunFire C18, 4.6X150 mm, 3.5 μm
Start %B = 10
Final %B = 100
Gradient time = 15 min
Stop time = 18 min
Flow Rate = 1 mL/min
Wavelength = 220 & 254 nm
Solvent A = 0.1% TFA in 5% CH_3CN/95%H_2O
Solvent B = 0.1% TFA in 95% CH_3CN/5% H_2O

Condition OL4b
Column = Waters Xbridge phenyl, 4.6X150 mm, 3 μm
Start %B = 10
Final %B = 50

Gradient time = 15 min
Stop time = 18 min
Flow Rate = 1 mL/min
Wavelength = 220 & 254 nm
Solvent A = 0.1% TFA in 5% CH_3CN/95%H_2O
Solvent B = 0.1% TFA in 95% CH_3CN/5% H_2O

Condition OL4c
Column = Waters Acquity BEH C18; 1.7 μm; 50 X 2.1 mm ID; (at 35 °C)
Hold 2%B = 0-1 min
2-98%B = 1-1.5 min
98%B = 1.5-2.2 min
Flow rate = 0.8 ml/min
Wavelength = 2 nm
Solvent A = 0.05% TFA in water
Solvent B = 0.05% TFA in CH_3CN

Condition OL5a
Column = PHENOMENEX® Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition OL5b
Column = PHENOMENEX® Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100

Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 10 mM NH_4OAc in 5% methanol/95%H_2O
Solvent B = 10 mM NH_4OAc in 95% methanol/5% H_2O

Condition-D4
Column = PHENOMENEX® Luna, 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition J4
Column = PHENOMENEX® Luna 4.6X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 4 min
Stop time = 5 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition PY1
Column = PHENOMENEX®, 2.0 X 50 mm, 3 μm
Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 0.8 mL/min

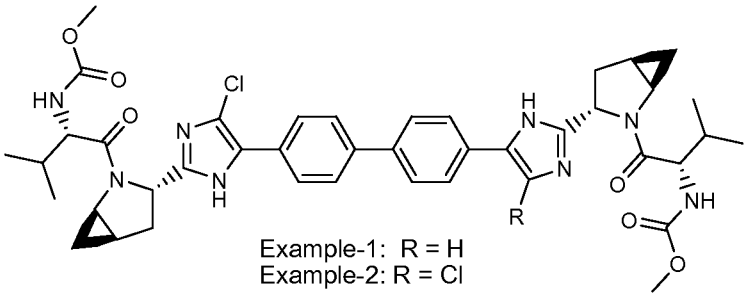
Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

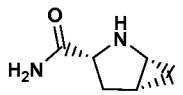
Solvent B = 0.1 % TFA in 90% methanol/10% water

Oven temp. = 40 °C

Examples 1 and 2

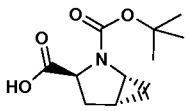


Example 1, Step a



[00371] Amide 1a (CH_3SO_3H) was prepared according to the procedure described for the synthesis of its enantiomer in patent WO 2004/052850.

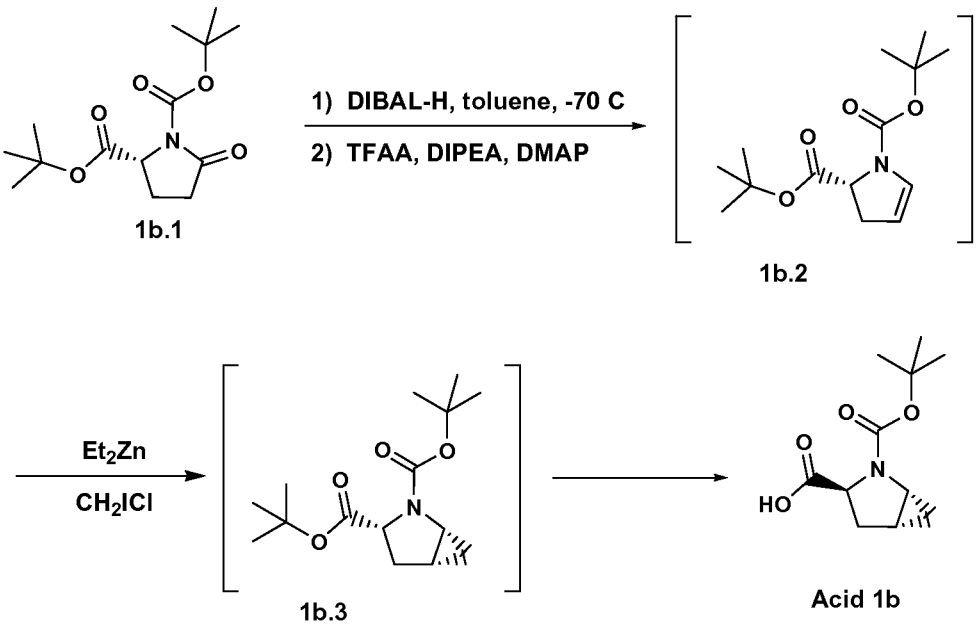
Example 1, Step b



[00372] A 1 L round bottom flask equipped with a nitrogen inlet, overhead agitator, thermocouple and heating mantle was charged with 50 g (225 mmol) amide 1a (.CH_3SO_3H) and 250 mL isopropanol. The resulting slurry was then charged with 252 mL of 23 wt% NaOEt in EtOH (2.68 M, 675 mmol, 3.0 equiv) and stirred at 50 °C for ca. 1h. The mixture was charged with 12.2 mL (675 mmol, 3 equiv) of water and heated to

60 °C. The resulting slurry was allowed to stir at 60 °C for ca. 18h. The slurry was cooled to rt and charged with 250 mL water and 98.2 g (450 mmol, 2.0 equiv) di-*t*-butyldicarbonate. Ethanol and isopropanol were removed *via* vacuum distillation and the aqueous mixture cooled to 0 °C. The mixture was neutralized with 76 mL (456 mmol) 6M aqueous HCl while maintaining an internal temperature < 5 °C. The product was extracted with 500 mL MTBE and the rich organic layer was washed with 100 mL water. The clear solution was concentrated down to 150 mL *via* vacuum distillation and the resulting slurry was charged with 600 mL heptane while maintaining an internal temperature > 45 °C. The slurry was cooled to rt over ca. 30 min and allowed to stir at rt for ca. 2h. The product was filtered, washed with 250 mL 4:1 heptane:MTBE and dried under vacuum at 70 °C to give 40.5 g (178 mmol, 79% yield, 99.8 AP at 205 nm) of acid 1b: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 4.02-3.80 (m, 1H), 3.45-3.15 (m, 1H), 2.40-2.19 (m, 1H), 2.19-2.0 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1.20 (m, 9H), 0.83-0.60 (m, 1H), 0.33-0.55 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 173.2, 155.0, 154.3, 79.4, 60.5, 60.2, 37.6, 32.6, 31.8, 28.4, 28.2, 15.6, 15.2, 14.4; HRMS calcd for $C_{11}H_{18}NO_4$ (M + H; ESI$^+$): 228.1236. Found: 228.1234.

Alternative synthesis of acid 1b



[00373] In a 500-mL reactor ester 1b.1 (commercially available, 17.5 g, 1.00 equiv) was dissolved in THF (87.5 mL). The resulting solution was cooled to -75 °C and 1.5M

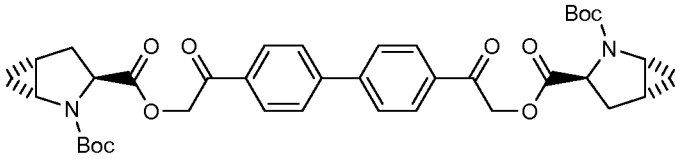
DIBAL-H in toluene (61.3 mL, 1.5 equiv) was charged while maintaining the temperature below -70 °C. The resulting solution was stirred at -70 °C for 1 hour. Trifluoroacetic acid (2.3 mL, 0.5 equiv) was charged over 10 minutes maintaining the internal temperature below -70 °C. Triethylamine (51.3 mL, 6 equiv) was then charged over 15 minutes maintaining the internal temperature below -70 °C. Trifluoroacetic anhydride (11.2 mL, 1.3 equiv) was charged over 10 minutes maintaining the internal temperature below -70 °C. The reaction was then allowed to warm to room temperature over 90 minutes and quenched *via* inverse addition to a solution of 20 wt % aqueous citric acid monohydrate (96.6 g, 1.5 equiv) while maintaining a temperature below 15 °C. The resulting mixture was stirred at room temperature for 2 hours then the lower aqueous layer was discarded. The product rich organic layer was washed twice with 70 mL saturated aqueous sodium bicarbonate. Solid sodium bicarbonate (1.7 g, 0.1 g/g Example 146) was charged and the solution was solvent exchanged into pure toluene under vacuum to provide 1b.2 as a solution in 2 L/kg toluene.

[00374] A solution of 1b.2 (16.5g theoretical from Example 151) in 33 mL toluene was polish filtered into a 250 mL reactor. Trifluorotoluene (50 mL) and chloroiodomethane (43.2 g, 4.0 equiv) were then charged and the resulting solution cooled to -20 °C. 1.1M Diethylzinc in toluene (111 mL, 2.0 equiv) was charged while maintaining the internal temperature < -8 °C. The resulting solution was stirred at -15 to -20 °C for 14 hours. The reaction mixture was warmed to 0 °C then quenched via inverse addition to a solution of 20 wt % aqueous citric acid (135.7 g, 2.3 equiv). The reactor was rinsed with toluene (82 mL) and the rinse added to the quench solution. The resulting biphasic mixture was stirred for 20 minutes then the lower aqueous layer was split and discarded. The rich organic was washed twice with 60 mL 13 wt % aqueous NaCl followed by 60 mL saturated $NaHCO_3$. The resulting solution was solvent exchanged into pure IPA under vacuum to provide 1b.3 as a solution in 10 L/kg IPA.

[00375] A 250mL reactor was charged with a solution of 1b.3 (147 mL, 14.7g theoretical from ester 1b.1) in IPA. The solution was warmed to 35 °C and solid sodium hydroxide (6.2 g, 3.0 equiv) was added. The resulting mixture was stirred at 35 °C overnight. Water (44 mL) was added and the organic solvents removed under vacuum. MTBE (145 ml) was added and the pH adjusted to 3.0 with 6N aqueous HCl. The aqueous layer was split and discarded. The product rich organic was washed with 60 mL

water then azeotropically dried under vacuum *via* constant volume addition of MTBE. The solution was concentrated to 55 mL and stirred at 50 °C for 30 minutes. The solution was cooled to room temperature over 1 hour during which time a slurry formed. Heptane (90 mL) was charged over 90 min and the resulting slurry aged for 1h. The solids were collected on a medium glass frit and washed with 22.5 mL 3:1 heptane:MTBE followed by 22.5 mL heptane. The tan solid was dried in a 50 °C vacuum oven to provide 5.48 g (46%) acid 1b with 94.9 LCAP purity. The crude acid 1b was dissolved in 55 mL MTBE at 50 °C. The resulting solution was concentrated to 20 mL and cooled to room temperature over 1 hour. Heptane (33mL) was then added over 90 minutes. The resulting solids were collected on a medium glass frit, washed with heptane (15mL), and dried in a 50 °C vacuum oven to provide 4.45 g of acid 1b as a tan powder (98.8 AP, 98.8% chiral purity, 37% from ester 1b.1).

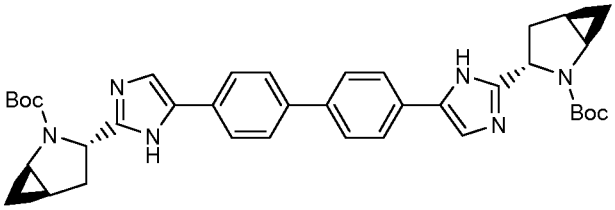
Example 1, Step c



[00376] A 250 mL round bottom flask equipped with a nitrogen inlet, overhead agitator and thermocouple was charged with 20.0 g (88.0 mmol, 2.11 equiv) acid 1b, 16.5 g (41.7 mmol, 1 equiv) 1,1′-(biphenyl-4,4′-diyl)bis(2-bromoethanone), 110 mL acetonitrile and 55 mL tetrahydrofuran. Diisopropylethylamine (15.1 mL, 86.6 mmol, 2.08 equiv) was then charged while maintaining an internal temperature < 25 °C. The mixture was allowed to stir at 20-25 °C for ca. 5h and charged with 83 mL ethyl acetate and 90 mL 13 wt% aqueous NaCl. The resulting biphasic mixture was separated and the rich organic layer was washed with an additional 90 mL 13 wt% aqueous NaCl. The rich organic layer was diluted with 20 mL tetrahydrofuran and washed with an aqueous mixture of $NaHCO_3$ and NaCl (45 mL 1M aqueous $NaHCO_3$ and 45 mL 26% aqueous NaCl). The rich organic layer was solvent exchanged into toluene *via* vacuum distillation to a target volume of ca. 160 mL. The resulting toluene solution of ketoester 1c was used as is in the next step.

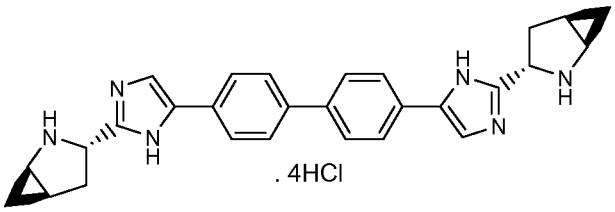
[00377] [Note: for the preparation of 1,1′-(biphenyl-4,4′-diyl)bis(2-bromoethanone), see process patent application WO 2009/020825].

Example 1, Step d



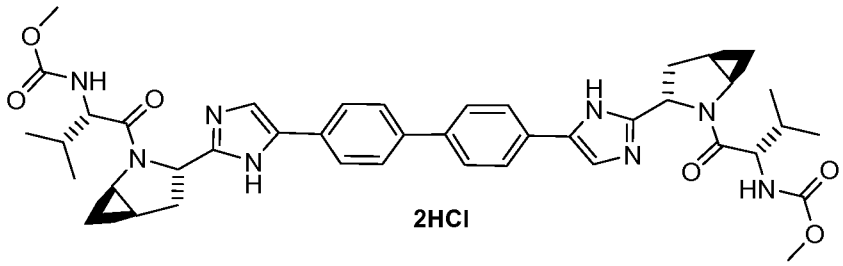
[00378] The above toluene solution of ketoester 1c was charged with 64.2 g (832.9 mmol, 20.0 equiv) NH_4OAc and allowed to stir at 90-100 °C for ca. 18h. Cooled to 60 °C and charged 255 mL 2:1 AcOH:water. The resulting biphasic mixture was separated and the toluene layer was washed with 58 mL 1:1 AcOH:water. The rich aqueous layers were combined and residual toluene was removed *via* vacuum distillation. The aqueous solution was diluted with 60 mL methanol and heated to 50-60 °C. Charged 106 mL (1060 mmol, 25.4 equiv) 10 N NaOH while maintaining an internal temperature < 60 °C. The resulting slurry was then cooled to rt. The slurry was filtered and washed with 100 mL water followed by 400 mL methanol to give 26.1 g of crude imidazole 1d. The wet, crude imidazole 1d was then charged into a 500 mL round bottom flask equipped with a nitrogen inlet, overhead agitator and thermocouple. Charged 165 mL N-methyl-2-pyrrolidinone and heated to 50 °C. The resulting clear solution was charged with 30 mL Methanol and allowed to stir at 50 °C for ca. 18h. The resulting slurry was charged with an additional 130 mL methanol while maintaining an internal temperature > 45 °C. The slurry was allowed to stir at 50 °C for ca. 30 min and cooled to rt. The slurry was filtered and the solids were washed with 90 mL 1:1 methanol:N-methyl-2-pyrrolidinone followed by 200 mL methanol. The solids were dried under vacuum at 70 °C to give 22.7 g (31.5 mmol, 76% yield, 95 AP at 254nm) imidazole 1d: ^1H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 2H), 7.89-7.76 (d, 4H), 7.74-7.60 (d, 4H), 7.50 (s, 2H) 4.62 (s, 2H), 3.55-3.30 (m, 2H), 2.45-2.20 (m, 4H), 1.70-1.59 (m, 2H), 1.59-0.90 (s, 18H), 0.83-0.69 (m, 2H), 0.65-0.49 (m, 2H); HRMS calcd for $C_{38}H_{45}N_6O_4$ (M + H; ESI^+): 649.3502. Found: 649.3524.

Example 1, Step e



[00379] A 250 mL round bottom flask equipped with a nitrogen inlet and overhead agitator was charged with 7.0 g (10.8 mmol) imidazole 1d, 105 mL methanol and 3.7 mL (20.8 mmol, 1.93 equiv) 5.6 M HCl in isopropanol. The resulting solution was treated with charcoal and filtered. The charcoal was washed with 140 mL methanol and combined with the filtrate. The rich organic stream was concentrated down to ca. 70 mL and charged into a round bottom flask equipped with a nitrogen inlet, overhead agitator and thermocouple. The solution was then charged with 14.75 mL (88.5 mmol, 8.2 equiv) 6M HCl and allowed to stir at 50 °C. After ca. 12h at 50 °C, the mixture was charged with 50 mL isopropanol and the resulting slurry was allowed to stir at 50 °C for 1h. The slurry was cooled to rt and aged for ca. 15h. The product was filtered and washed with 35 mL 4:1 isopropanol:methanol followed by 70 mL isopropanol. The solids were dried at 55 °C under vacuum to give 5.3 g (8.9 mmol, 83%, 99.8 AP at 254 nm) pyrrolidine 1e/4HCl: ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.00-9.38 (bs, 8H), 8.31 (s, 2H), 8.06-7.96 (d, 4H), 7.94-7.84 (d, 4H), 5.05-4.89 (dd, 2H), 3.55-3.42 (m, 2H), 2.87-2.69 (dt, 2H), 2.64-2.53 (dd, 2H), 2.05-1.89 (m, 2H), 1.17-0.98 (m, 2H), 0.96-0.82 (dd, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.0, 139.3, 133.6, 127.2, 126.6, 125.8, 116.6, 49.8, 34.3, 29.9, 15.2, 5.3; HRMS calcd for $C_{28}H_{29}N_6$ (M + H; ESI$^+$): 449.2454. Found: 449.2470.

Example 1, Step f



[00380] A 250 mL jacketed reactor equipped with a nitrogen inlet, overhead agitator and thermocouple was charged with 4.24 g (24.2 mmol, 2.4 equiv) (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid, 3.86 g (25.21 mmol, 2.5 equiv) 1-

hydroxybenzotriazole monohydrate, 4.55 g (23.73 mmol, 2.35 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 60 mL acetonitrile. The mixture was stirred for ca. 1h and charged with 6 g (10.1 mmol) pyrrolidine 1e/4HCl. The resulting slurry was cooled to 10 °C and charged with 7.92 mL (45.41 mmol, 4.5 equiv) diisopropylethylamine. The mixture was allowed to warm to rt and stirred for ca. 19h. The resulting organic solution was washed with 36 mL 13 wt% aqueous NaCl. The rich organic was charged with 12 mL acetonitrile and washed with 36 mL of an aqueous solution containing 13 wt% aqueous NaCl and 1 M NaOH. The rich organic was then charged with 12 mL methanol and heated to 50 °C. Water (60 mL) was added over a period of 2h and the resulting slurry was cooled to rt and aged for ca. 2h. The solids were filtered, washed with 36 mL 1:1 acetonitrile:water and dried under vacuum. A 250 mL jacketed reactor equipped with a nitrogen inlet, overhead agitator and thermocouple was charged with the above solids and dissolved with 240 mL SDA3A grade ethanol. The solution was concentrated down to ca. 50 mL *via* vacuum distillation and charged with 4.24 mL (23.19 mmol, 2.30 equiv) 5.47 M HCl in isopropanol and an additional 30 mL SDA3A ethanol. The mixture was concentrated to ca. 50 mL, diluted with 40 mL SDA3A ethanol and treated with charcoal. The charcoal was filtered and washed with 90 mL SDA3A ethanol. The rich filtrate and wash were combined and concentrated down to 40 mL. Charged 16 mL ethyl acetate and heated to 40 °C. Charged 60 mg amide 1f/2HCl seed crystals and stirred at 40 °C for 1h. Charged an additional 68 mL ethyl acetate over 1.5h while maintaining an internal temperature of 40 °C. Stirred the resulting slurry at 40 °C for ca. 18h and cooled to rt. The slurry was filtered and washed with 24 mL 3:1 ethyl acetate:SDA3A ethanol and 30 mL ethyl acetate. The solids were dried under vacuum at 50 °C to give 6.83 g (8.17 mmol, 81%, 99.5 AP at 300 nm) amide 1f/2HCl: ^{1}H NMR (600 MHz, DMSO-d_6) δ 15.51 (s, 2H), 14.95 (s, 2H) 8.19 (s, 2H), 8.05 (d, 4H), 7.91 (d, 4H), 7.25 (d, 2H), 5.18 (t, 2H), 4.44 (t, 2H), 3.77 (s, 2H), 3.55 (s, 6H), 2.50 (m, 2H), 2.39 (m, 2H), 2.24 (m, 2H), 1.91 (m, 2H), 0.95 (m, 2H), 0.92 (d, 6H), 0.81 (d, 6H), 0.75 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.7, 156.9, 148.5, 139.1, 131.7, 127.1, 126.5, 125.9, 115.1, 57.8, 54.5, 51.5, 37.3, 32.9, 29.2, 19.7, 17.5, 17.5, 15.7; Calculated Elemental Analysis (corrected for 0.81% water): C = 59.86%, H = 6.30%, N = 13.29%, Cl = 8.41%; Found: C = 59.99%, H = 6.27%, N = 13.12%, Cl = 8.42%.

[00381] Preparation of Seed for amide 1f/2HCl: Amide 1f was prepared according to the basic procedure outlined above using 504 mg (0.8 mmol) pyrrolidine 1e.4HCl. After reaction completion, the rich acetonitrile solution was washed with 3 mL 13% aqueous NaCl, 2x 3 mL of an aqueous solution containing 13% NaCl and 1M NaOH, and 3 mL 13% aqueous NaCl. The rich organic was concentrated down to a residue and diluted with 10 mL acetonitrile. The hazy mixture was filtered and the clear filtrate was concentrated down to a residue. The residue was diluted with 10 mL SDA3A ethanol and charged with 2.1 mL (1.9 mmol, 2.4 equiv) 0.88 M HCl in ethanol. The mixture was concentrated down to a residue and diluted with 1.8 mL isopropanol. The resulting solution was heated to 50 °C and allowed to stir for ca. 18h. The resulting slurry was cooled to rt, filtered and washed with 2:1 acetone:ethanol to give 476 mg (0.57 mmol, 78%) amide 1f/2HCl.

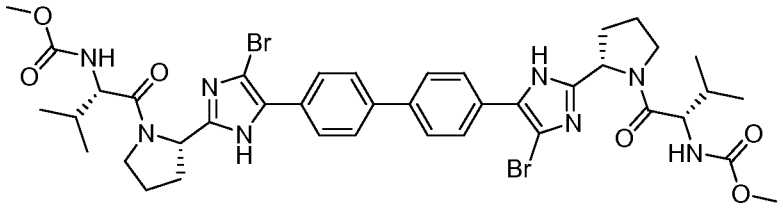
[00382] [Note: (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid was purchased from Flamma.]

Examples 1 and 2

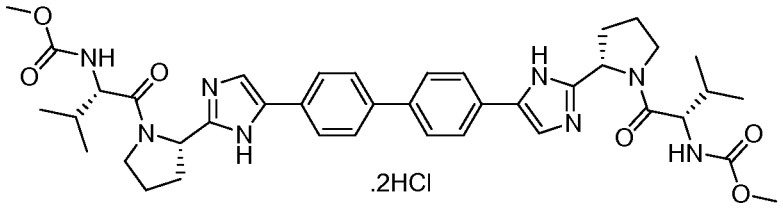
[00383] A sample of amide1f/2HCl (106.9 mg) was free-based (2 g MCX column; MeOH wash; 2 N NH_3/MeOH elution) and dried *in vacuo*. NCS (0.0195 g, 0.146 mmol) was added to a DMF (2.5 mL) solution of the resultant material and heated with an oil bath at 50 °C for 16.5 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salts of Example 1 (white foam; 56.1 mg) and Example 2 (white foam; 22.3 mg). Example 1: ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): 12.61 (br s, 1H), 8.13 (s, 1H), 7.93 (d, J = 8.5, 2H), 7.90-7.86 (m, 4H), 7.82 (d, J = 8.5, 2H), 7.27 (d, J = 8.3, 1H), 7.17 (d, J = 8.5, 1H), 5.02-4.94 (m, 2H), 4.44-4.38 (m, 1.80H), 4.31 (app br s, 0.2H), 3.75 (m, 1H), 3.62 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 2.56-2.50 ('m' partially overlapped with solvent signal, 1H), 2.41-2.23 (m, 3H), 2.17-2.09 (m, 1H), 2.07-2.00 (m, 1H), 1.97-1.91 (m, 1H), 1.88-1.81 (m, 1H), 1.01-0.81 (m, 15H), 0.71 (m, 1H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. 1a): R_t = 1.80 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}ClN_8O_6$: 797.35; found 797.33. Example 2: ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): 7.86 (d, J = 8.6, 4H), 7.80 (d, J = 8.5, 4H), 7.17 (d, J = 8.5, 2H), 4.96

(dd, J = 7.5, 6.0, 2H), 4.40 (app t, J = 7.8, 2H), 3.61 (m, 2H), 3.54 (s, 6H), 2.33-2.23 (m, 4H), 2.09-1.98 (m, 2H), 1.90-1.82 (m, 2H), 1.01-0.82 (overlapped 'm' and two 'd' at 0.96 ppm and 0.87 ppm with J = 6.8 and J = 6.5, respectively; 14H); 0.71 (m, 1.7H), 0.62 (m, 0.3H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. 1a): R_t = 2.79 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}Cl_2N_8O_6$: 831.32; found 831.26.

Example 3



Example 3, Step a

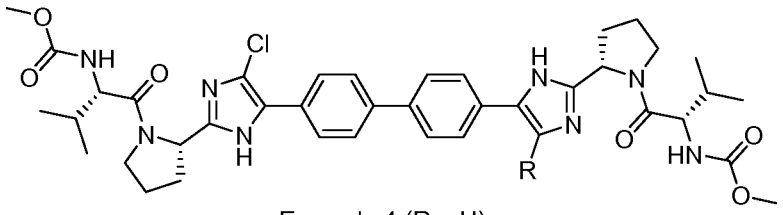


[00384] For the synthesis of amide 3a/2HCl, see the process patent application WO 2009/020825.

Example 3

[00385] To a solution of amide 3a (32 mg, 0.043 mmol) in acetic acid (2 mL) was added 2 eqv. of 1M bromine in acetic acid and the reaction was stirred for 30 min. An additional 1 eqv. bromine was added (solids formed), and the reaction was neutralized with 5% $NaHCO_3$ and extracted with EtOAc (2x10 mL). The combined extracts were washed with sat'd $Na_2S_2O_3$ soln and brine and concentrated. The residue was dried under high vacuum to afford Example 3 (41 mg). LC-MS (Cond.-J4): RT = 3.54 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}Br_2N_8O_6$: 897.22; found 897.28.

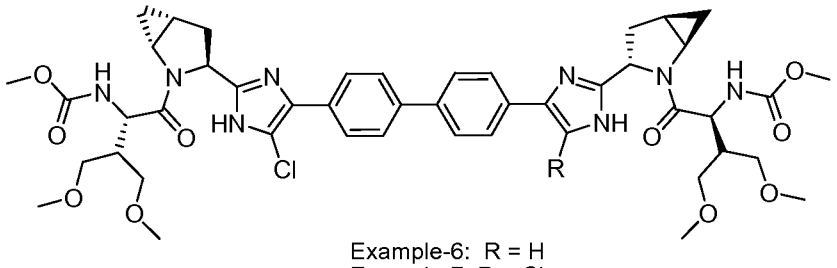
Examples 4 and 5



Example 4 (R = H)
Example 5 (R = Cl)

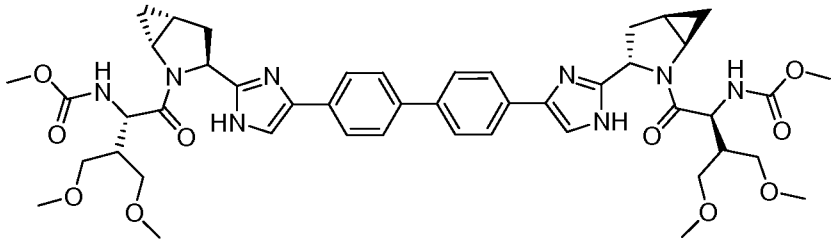
[00386] Diisopropylethyl amine (100 ul, 74.2 mg, 0.574 mmol) was added to a mixture of amide 3a (197mg, 0.243 mmol) and N-chlorosuccinamide (39 mg, 0.292 mmol) in acetonitrile (2 mL) and stirred for overnight. An additional portion of N-chlorosuccinamide (66mg, 0.494 mmol) was then added to the reaction mixture and stirred until the consumption of the starting material was confirmed by HPLC analysis. The crude reaction mixture was then purified by reverse phase HPLC (Solvent A = H_2O/CH_3CN (95:5) + 0.05% TFA; Solvent B = H_2O/CH_3CN (5:95) + 0.05% TFA; Column: Luna C18, 5u, 100 × 21.5 mm; Flow rate: 20 mL/min) to afford the TFA salts of Example 4 (yellowish amorphous powder, 60 mg) and Example 3 (yellowish amorphous powder, 115 mg). Example 5: LC-MS (Cond. 3): R_t = 6.13 min. ^{1}H NMR (DMSO-d_6, TMS, 600 MHz): 8.16 (s, 1H), 7.95-7.91 (m, 7H), 7.85 (d, *J* = 8.8, 2H), 7.35 (d, *J* = 8.4, 1H), 7.32 (d, *J* = 8.4, 1H), 5.19 (t, *J* = 7.3, 1H), 5.05 (m, 1H), 4.15 (t, *J* = 7.7, 1H). 4.08 (t, *J* = 8.1, 1H), 3.88-3.81 (m, 4H), 3.56 (s, 6H), 2.43 (m, 1H), 2.21-2.11 (m, 4H), 2.08-2.05 (m, 2H), 1.97 (m, 3H), 0.91 (d, *J* = 6.5, 3H), 0.87 (d, *J* = 7.0, 3H), 0.85 (d, *J* = 7.0, 3H), 0.80 (d, *J* = 6.6, 3H). HRMS: Calcd. for $[M+H]^+$ $C_{40}H_{50}ClN_8O_6$: 773.3542; found 773.3530. Example 4: LC-MS (Cond. 3): R_t = 8.61 min. ^{1}H NMR (DMSO-d_6, TMS, 600 MHz): 7.89 (d, *J* = 8.3, 4H), 7.83 (d, *J* = 8.3, 4H), 7.33 (d, *J* = 8.4, 2H), 5.05 (m, 2H), 4.09 (t, *J* = 8.3, 2H), 3.84-3.81 (m, 4H), 3.56 (s, 6H), 2.24-2.15 (m, 4H), 2.00-1.95 (m, 6H), 0.91 (d, *J* = 6.7, 6H), 0.87 (d, *J* = 6.6, 6H). HRMS: Calcd. for $[M+H]^+$ $C_{40}H_{49}Cl_2N_8O_6$: 807.3152; found 807.3138.

Examples 6 and 7



Example-6: R = H
Example-7: R = Cl

Example 6, Step a



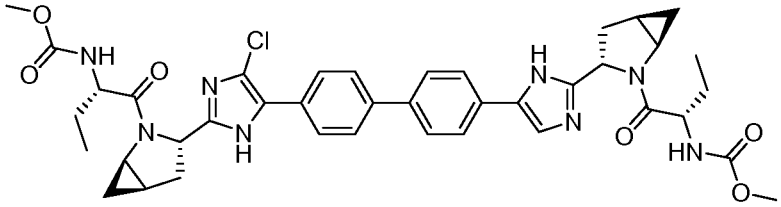
[00387] To a mixture of pyrrolidine 1e/4HCl (0.104 g, 0.174 mmol), HATU (0.133 g, 0.349 mmol) and Cap-193 (0.082 g, 0.349 mmol) in DMF was added DIEA (0.183 mL). The reaction mixture was stirred at room temperature for 3 hrs. The reaction mixture was purified by preparatory HPLC (PHENOMENEX® Axia 5 u column, 35 min gradient from 0-90%B. A = H_2O/CH_3CN/10 mM NH_4OAc, 95:5. B = CH_3CN/H_2O/10 mM NH_4OAc 95:5) to afford Example 6, Step a (0.064 g). LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{59}N_8O_{10}$: 883.43; found: 883.26. ^1H NMR (400 MHz, MeOD) ppm 7.90 (2 H, s), 7.78 - 7.86 (8 H, m), 5.13 (2 H, dd, *J*=9.2, 6.9 Hz), 4.96 (2 H, d, *J*=5.0 Hz), 3.73 - 3.79 (2 H, m), 3.63 (6 H, s), 3.39 - 3.49 (6 H, m), 3.35 (1 H, d, *J*=4.8 Hz), 3.32 - 3.34 (1 H, m), 3.30 (6 H, s), 3.15 (6 H, s), 2.66 (2 H, dd, *J*=13.5, 9.4 Hz), 2.37 - 2.51 (4 H, m), 2.02 - 2.09 (2 H, m), 1.03 - 1.14 (2 H, m), 0.81 - 0.93 (2 H, m).

Examples 6 and 7

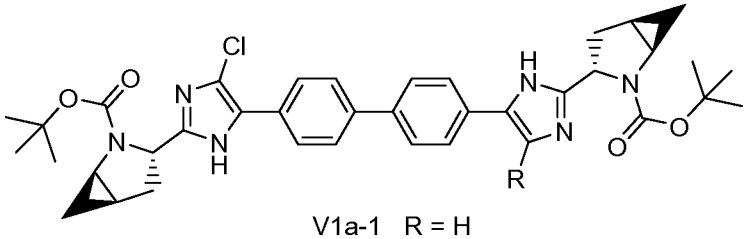
[00388] To a solution of Example 6, Step a (0.057 g) in DMF was added NCS (10.34 mg, 0.077 mmol). The reaction mixture was heated at 60 °C for 3 hrs. The reaction mixture was purified by preparatory HPLC (PHENOMENEX® Axia 5 u 30 x 100 mm column, 20 min gradient from 0-100%B. A = H_2O/CH_3OH/TFA 90:10:0.1. B = CH_3OH/H_2O/TFA 90:10:0.1) to afford Example 6 (0.022 g) and Example 7 (0.017 g). Example 6: LC (Cond.-J5): R_t = 3.46 min. LC-MS: Anal. Calcd. For $[M+H]^+$

$C_{46}H_{58}ClN_8O_{10}$: 917.39; found: 917.12. ^{1}H NMR (400 MHz, MeOD) ppm 7.87 - 7.91 (1 H, m), 7.77 - 7.86 (8 H, m), 5.14 (1 H, dd, *J*=9.2, 6.9 Hz), 5.05 (1 H, dd, *J*=8.1, 6.3 Hz), 4.96 (2 H, t, *J*=5.7 Hz), 3.73 - 3.79 (1 H, m), 3.67 - 3.72 (1 H, m), 3.57 - 3.66 (6 H, m), 3.32 - 3.51 (8 H, m), 3.29 (6 H, d, *J*=1.8 Hz), 3.19 (3 H, s), 3.12 - 3.16 (3 H, m), 2.60 - 2.72 (1 H, m), 2.32 - 2.54 (5 H, m), 2.02 (2 H, d, *J*=6.3 Hz), 1.00 - 1.19 (2 H, m), 0.88 (1 H, br. s.), 0.82 (1 H, br. s.). Example 7: LC (Cond. PY1): R_t = 4.083 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{56}Cl_2N_8O_{10}$: 951.35; found: 951.09. ^{1}H NMR (400 MHz, MeOD) ppm 7.74 - 7.84 (8 H, m), 5.05 (2 H, t, *J*=7.2 Hz), 4.95 (2 H, d, *J*=5.5 Hz), 3.66 - 3.72 (2 H, m), 3.63 (6 H, s), 3.37 - 3.53 (8 H, m), 3.30 (6 H, s), 3.19 (6 H, s), 2.32 - 2.51 (6 H, m), 1.92 - 2.06 (2 H, m), 1.08 (2 H, dt, *J*=8.6, 5.8 Hz), 0.81 (2 H, d, *J*=1.8 Hz).

Example V1



Example V1, Step a

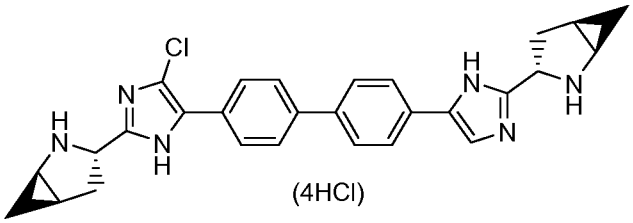


V1a-1 R = H
V1a-2 R = Cl

[00389] A solution of carbamate 1d (0.80 g, 1.23 mmol) and NCS (0.214 g, 1.603 mmol) in DMF (12 mL) was heated at 50 °C for 17h. After it was allowed to cool to ambient temperature, volatile components were removed *in vacuo*. The residue was dissolved in MeOH (36 mL) and the two products were separated by prep-HPLC (Column: XTERRA®, 30 X 100 mm, S5; Start %B = 50, Final %B = 100; Gradient time = 10 min; Stop time = 12 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% MeOH – 90% H_2O – 0.1% TFA; Solvent B = 90% MeOH – 10% H_2O – 0.1% TFA). Each of the two fractions were neutralized with an excess solution of 2N NH_3/MeOH and

concentrated *in vacuo* to remove most of the methanol, and the residue was partitioned between 20% MeOH/$CHCl_3$ and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford chloride V1a-1 (light yellow foam; 288.4 mg) and dichloride V1a-2 (light yellow solid; 400.4 mg). Chloride V1a-1: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.62-12.60 (m, 1H), 12.23 (s, 0.2H), 11.92 (s, 0.8H), 7.85-7.32 (m, 9H), 4.68-4.42 (m, 2H), 3.47-3.38 (m, 2H), 2.40-2.35 (m, 2H), 2.26-2.20 (m, 2H), 1.71-1.58 (m, 2H), 1.55-0.96 (app br s, 18H), 0.82-0.69 (m, 2H), 0.64-0.51 (m, 2H). LC (V-Cond. 1): R_t = 2.44 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{44}ClN_6O_4$: 683.31; found: 683.31. Dichloride V1a-2: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.62 (s, 2H), 7.85 (d, *J* = 8.8, 4H), 7.82 (d, *J* = 8.9, 4H), 4.61-4.42 (m, 2H), 3.53-3.38 (m, 2H), 2.41-2.35 (m, 2H), 2.27-2.20 (m, 2H), 1.70-1.59 (m, 2H), 1.53-0.94 (app br s, 18H), 0.80-0.70 (m, 2H), 0.64-0.53 (m, 2H). LC (Cond. 1a): R_t = 2.89 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{38}H_{43}Cl_2N_6O_4$: 717.27; found: 717.31.

Example V1, Step b



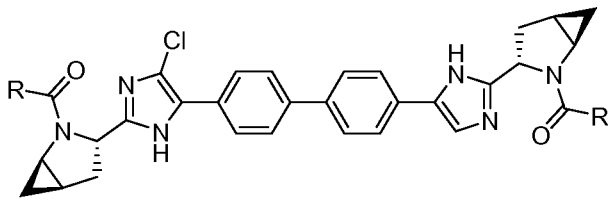
[00390] To a suspension of chloride V1a-1 (0.2741 g, 0.401 mmol) in MeOH (1 mL) was added 4M HCl in dioxane (4 mL). The mixture was stirred at room temperature for 7h, and then the volatile component was removed *in vacuo* to afford the HCl salt of V1b as a tan solid (231.7 mg). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 13.51 (br s, 1H), 10.53-10.30 (m, 2H), 9.87-9.72 (m, 1H), 8.02-7.85 (m, 9H), 4.72-4.68 (m, 1H), 4.65-4.53 (m, 1H), 3.42-3.30 (m, 2H), 2.68-2.37 ('m' partially overlapped with solvent signal, 4H), 1.97-1.87 (m, 2H), 1.16-1.07 (m, 2H), 0.89- 0.80 (m, 2H). LC (Cond. 1a): R_t = 1.66 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{28}ClN_6$: 483.21; found: 483.20. [Note: the exact HCl content of the product was not determined].

Example V1

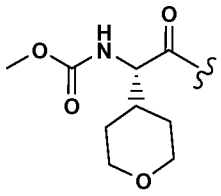
[00391] To a solution of chloride V1b/4HCl (0.045 g, 0.072 mmol), (S)-2-(methoxycarbonylamino)butanoic acid (0.025 g, 0.157 mmol), and N,N-diisopropylethylamine (0.075 mL, 0.429 mmol) in DMF (1.5 mL) was added HATU (0.057 g, 0.150 mmol). The reaction mixture was stirred at ~25 °C for 1h. It was diluted with MeOH (2.5 mL) and the product was purified by prep-HPLC (Column: XTERRA®, 30 X 100 mm, S5; Start %B = 30, Final %B = 90; Gradient time = 10 min; Stop time = 12 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% MeOH – 90% H_2O – 0.1% TFA; Solvent B = 90% MeOH – 10% H_2O – 0.1% TFA) to afford the TFA salts of Example V1 as a light yellow solid (39.4 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.80-14.36 (br m, 1.4H), 12.58 (app br s, 0.6H), 8.14 (s, 1H), 7.94 (d, *J* = 8.5, 2H), 7.89 (d, *J* = 8.3, 2H), 7.87 (d, *J* = 8.4, 2H), 7.82 (d, *J* = 8.6, 2H), 7.38 (d, *J* = 7.8, 0.9H), 7.28 (d, *J* = 7.8, 0.9H), 7.07 (app br s, 0.1H), 6.96 (app br s, 0.1H), 5.02 (dd, *J* = 8.8, 6.8, 1H), 4.96 (dd, *J* = 7.0, 6.0, 1H), 4.50-4.39 (m, 2H), 3.74-3.67 (m, 1H), 3.59-3.48 (m, 7H), 2.60-2.47 ('m' partially overlapped with solvent signal, 1H), 2.42-2.22 (m, 3H), 2.01-1.65 (m, 4H), 1.65-1.52 (m, 2H), 1.06-0.84 (m, 8H), 0.83-0.77, (m, 1H), 0.74-0.66 (m, 1H). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): R_t = 1.66 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{46}ClN_8O_6$: 769.32; found: 769.35.

Example V2

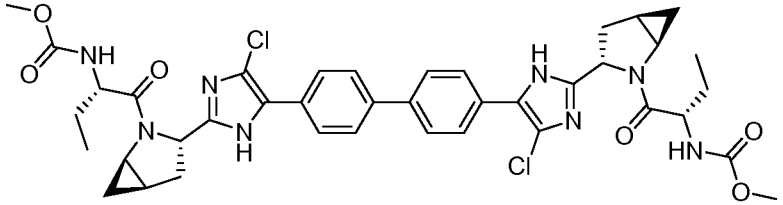
[00392] Example V2 (TFA salt) was prepared from pyrrolidine V1b/4HCl and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid according to the procedure described for the synthesis of Example V1.



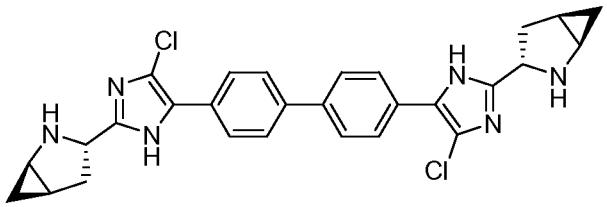
Example		R_t (LC-Cond.); LC (Cond. 2a and 2b): % homogeneity index; MS data

V2		2.06 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{54}ClN_8O_8$: 881.38; found: 881.36.

Example V3



Example V3, Step a



[00393] Intermediate V3a was prepared as HCl salt from carbamate V1a-2 according to the procedure described for the preparation of pyrrolidine V1b. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.62-10.48 (m, 2H), 9.92-9.75 (m, 2H), 7.92 (d, *J* = 8.8, 4H), 7.89 (d, *J* = 9.1, 4H), 4.68-4.57 (m, 2H), 3.40-3.31 (m, 2H), 2.54-2.50 ('m' partially overlapped with solvent signal, 2H), 2.46-2.39 (m, 2H), 1.91-1.85 (m, 2H), 1.16-1.07 (m, 2H), 0.85-080 (m, 2H). LC (Cond. 1a): R_t = 2.01 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{27}Cl_2N_6$: 517.17; found: 517.06. [Note: the exact HCl salt content of the product was not determined].

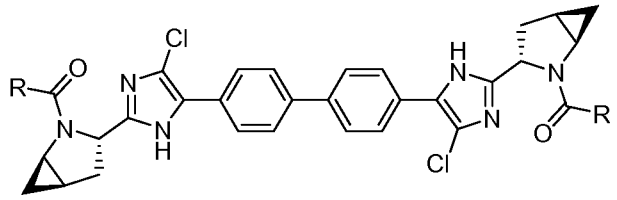
Example V3

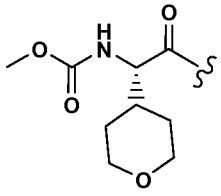
[00394] Example V3 (TFA salt) was prepared from the HCl salt of pyrrolidine V3a according to the procedure described for the synthesis of Example V1. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.59 (very br s, ~2H), 7.86 (d, *J* =8.5, 4H), 7.80 (d, *J* = 8.3, 4H), 7.46 (app br s, 0.13H), 7.37 (d, *J* = 7.6, 1.73H), 6.97 (app br s, 0.14H), 4.97-4.94 (m, 2H), 4.52-4.35 (m, 2H), 3.63-3.45 (m, 8H), 2.36-2.23 (m, 4H), 1.96-1.83 (m, 2H),

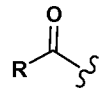
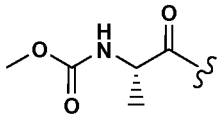
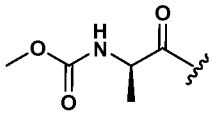
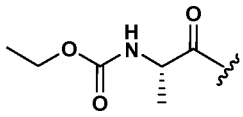
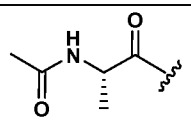
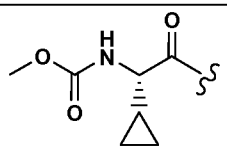
1.82-1.67 (m, 2H), 1.64-1.49 (m, 2H), 1.13-0.82 (m, 8H), 0.78-0.61 (m, 2H). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): R_t = 2.66 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}Cl_2N_8O_6$: 803.28; found: 803.28.

Examples V4 to V6

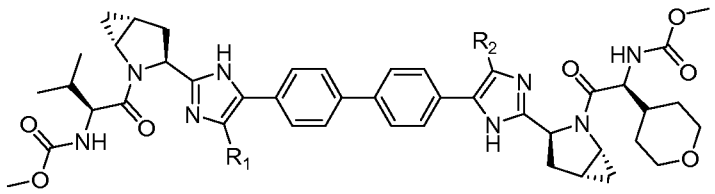
[00395] Examples V4 to V6 (TFA salt) were prepared from the HCl salt of pyrrolidine V3a and the appropriate acids according to the procedure described for the synthesis of Example V1.



Example		R_t (LC-Cond.); LC (Cond. 2a and 2b): % homogeneity index; MS data
V4		2.64 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}Cl_2N_8O_8$: 915.34; found: 915.70. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.63 (very br s, ~2H), 7.87 (d, *J* = 8.6, 4H), 7.78 (d, *J* = 8.5, 4H), 7.42 (app br s, 0.1H), 7.26 (d, *J* = 8.6, 1.75H), 6.97 (app br s, 0.14H), 4.95 (dd, *J* = 8.4, 5.1, 2H), 4.48 (app t, *J* = 8.1, 2H), 3.85 (m, 4H), 3.73-3.64 (m, 2H), 3.54 (s, 6H), 3.32-3.18 (m, 4H), 2.37-2.19 (m, 4H), 2.05-1.91 (m, 2H), 1.91-1.78 (m, 2H), 1.71-1.58 (m, 2H), 1.56-1.39 (m, 4H), 1.39-1.25, (m, 2H), 1.05-0.93 (m, 2H), 0.77-0.66 (m, 2H)

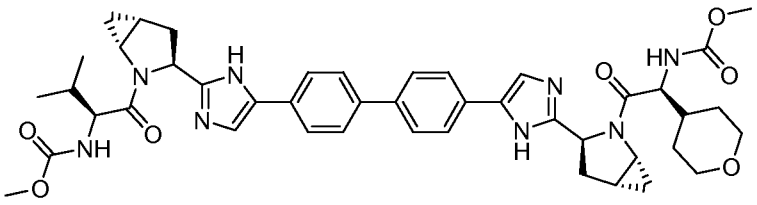
Example		R_t (LC-Cond.); LC (Cond. 2a and 2b): % homogeneity index; MS data
V5		2.59 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_6$: 775.25; found: 775.29. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.56 (very br s, ~2H), 7.86 (d, *J* = 8.5, 4H), 7.80 (d, *J* = 8.5, 4H), 7.37 (d, *J* = 7.6, 1.70H), 7.02 (app br s, 0.3H), 4.95 (app t, *J* = 6.8, 2H), 4.63-4.54 (m, 2H), 3.62-3.34 (overlapped 'm' and 's'; s is at 3.52; 8H), 2.31-2.28 (m, 4H), 1.91-1.84 (m, 2H), 1.28 (s, 3H). 1.27 (d, *J* = 7, 6H), 1.02-0.97 (m, 2H), 0.76-0.61 (m, 2H).
V5.1		2.65 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_6$: 775.25; found: 775.35.
V5.2		2.72 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}Cl_2N_8O_6$: 803.28; found: 803.38.
V5.3		2.50 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_4$: 743.26; found: 743.36.
V6		2.75 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}Cl_2N_8O_6$: 827.28; found: 827.33.

Examples V7 and V8



V7 (R_1 = H, R_2 = Cl)
V8 (R_1 = Cl, R_2 = H)

Example V7, Step a



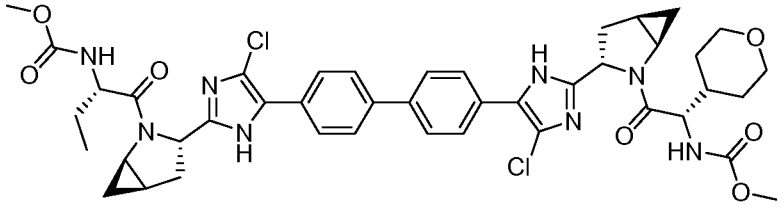
[00396] To a solution of pyrrolidine 1e/4HCl (0.350 g, 0.589 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.103 g, 0.589 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (0.128 g, 0.589 mmol) and N,N-diisopropylethylamine (0.720 mL, 4.12 mmol) in DMF (3 mL) was added HATU (0.493 g, 1.295 mmol). The reaction mixture was stirred at ~25 °C for 4 h, and then was diluted with MeOH and purified by prep-HPLC (Column: XTERRA®, 30 X 100 mm, S5; Start %B = 30, Final %B = 75; Gradient time = 15 min; Stop time = 15 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% MeOH – 90% H_2O – 0.1% TFA; Solvent B = 90% MeOH – 10% H_2O – 0.1% TFA) to isolate product V7a out of the three possible products. Product V7a was dissolved in MeOH and free-based (6g MCX cartridge; MeOH wash; 2N NH_3/MeOH elution) and concentrated *in vacuo* to afford a tan solid (103.2 mg). LC (Cond. 1a): R_t = 1.63 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_7$: 805.40; found: 805.49.

Examples V7 and V8

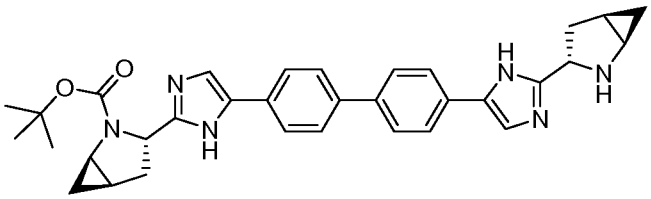
[00397] A solution of product V7a (0.103 g, 0.128 mmol) and NCS (0.022 g, 0.167 mmol) in DMF (1.5 mL) was heated at 50 °C for 24h. After it was allowed to cool to ambient temperature, the reaction mixture was diluted with MeOH and purified by prep-HPLC (Column: XTERRA®, 30 X 100 mm, S5; Start %B = 40, Final %B = 100; Gradient time = 15 min; Stop time = 17 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% MeOH – 90% H_2O – 0.1% TFA; Solvent B = 90% MeOH – 10% H_2O – 0.1% TFA) to isolate a mixture of regioisomers V7 and V8. The mixture was dissolved in MeOH and submitted to a different prep-HPLC purification condition (Column: Waters SunFire, 30 X 100 mm, S5; Start %B = 10, Final %B = 50; Gradient time = 20 min; Stop time = 20 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% Acetonitrile – 90% H_2O – 0.1% TFA; Solvent B = 90% Acetonitrile – 10% H_2O – 0.1%

TFA) to separate the two regioisomers as TFA salts. Example V7 (off-white solid, 17.3 mg): ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.52 (app br s, too broad to integrate), 12.64 (app br s, too broad to integrate), 8.14 (s, 1H), 7.95-7.79 (m, 8H), 7.26 (two overlapped 'd', *J* = ~8.6, 1.70H), 7.10 (app br s, 0.08H), 6.98 (app br s, 0.22H), 5.01-4.97 (m, 1H), 4.96-4.92 (m, 1H), 4.50-4.46 (m, 1H), 4.43-4.40 (m, 1H), 3.90-3.81 (m, 2H), 3.79-3.72 (m, 1H), 3.71-3.64 (m, 1H), 3.54 (app s, 6H), 3.31-3.18 (m, 2H), 2.65-2.50 ('m' partially overlapped with solvent, 1H), 2.45-2.19 (m, 3H), 2.18-2.08 (m, 1H), 2.04-1.89 (m, 2H), 1.89-1.79 (m, 1H), 1.69-1.59 (m, 1H), 1.55-1.41 (m, 2H), 1.38-1.23 (m,1H), 1.04-0.77 (m, 9H), 0.74-0.67 (m, 1H). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): R_t = 2.15 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}Cl_1N_8O_7$: 839.36; found: 839.35. Example V8 (off-white solid, 16.8 mg): ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.53 (br s, too broad to integrate), 12.61 (br s, too broad to integrate), 8.13 (s, 1H), 7.94 (d, *J* = 8.3, 2H), 7.90 (d, *J* = 8.6, 2H), 7.85 (d, *J* = 8.5, 2H), 7.82 (d, *J* = 8.6, 2H), 7.36 (d, *J* = 8.8, ~1H), 7.17 (d, *J* = 8.5, ~1H), 5.00-4.94 (m, 2H), 4.49 (app t, *J* = 7.7, 1H), 4.40 (app t, *J* = 7.9, 1H), 3.90-3.78 (m, 3H), 3.65-3.59 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 3.35-3.19 (m, 2H), 2.64-2.50 ('m' partially overlapped with solvent signal, 1H), 2.41-2.34 (m, 1H), 2.33-2.22 (m, 2H), 2.12-1.99 (m, 2H), 1.99-1.90 (m, 1H), 1.89-1.81 (m, 1H), 1.52-1.27 (m, 4H), 1.07-0.84 (m, 8H), 0.84-0.77 (m, 1H), 0.75-0.65 (m, 1H). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): R_t = 2.15 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}Cl_1N_8O_7$: 839.36; found: 839.38.

Example V9

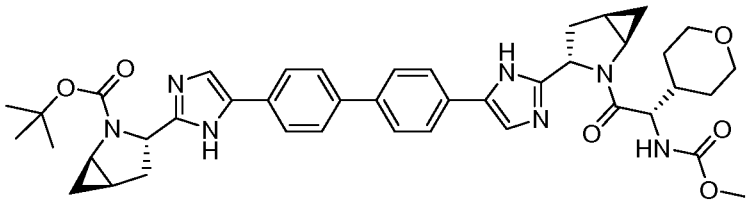


Example V9, Step a



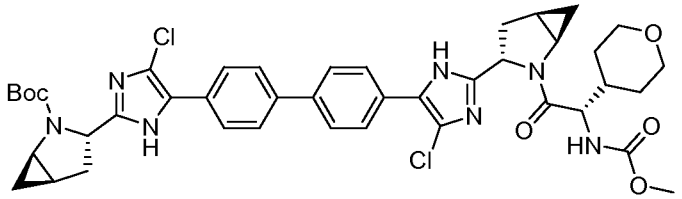
[00398] Boc_2O (0.734 g, 3.36 mmol) followed DMAP (0.021 g, 0.168 mmol) were added to a mixture of pyrrolidine 1e/4HCl (2.00 g, 3.36 mmol) and Et_3N (2.3 ml, 16.82 mmol) in DMF (60 ml), and stirred at ambient condition for 4.5 h. The volatile component was removed *in vacuo*, and the residue was partitioned between 1.0 N NaOH (20 mL) and 20% MeOH/$CHCl_3$ (50 mL). The aqueous phase was washed with 20% MeOH/$CHCl_3$ (50 mL, 2x). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. A silica gel mesh was prepared from the resultant crude material and submitted to a BIOTAGE® purification (160 g silica gel) where the column was first eluted with EtOAc until all of the higher R_f spot (*i.e.*, bis-Boc derivative 1d; 0.28 g) came out, and then the column was eluted with 5-10% MeOH/CH_2Cl_2 over 2.5 L to elute residual bis-Boc x (followed by mono-Boc V9a (0.81 g; ~containing 1.1 mol equiv of Et_3N). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{33}H_{37}N_6O_2$: 549.30; found 549.45.

Example V9, Step b



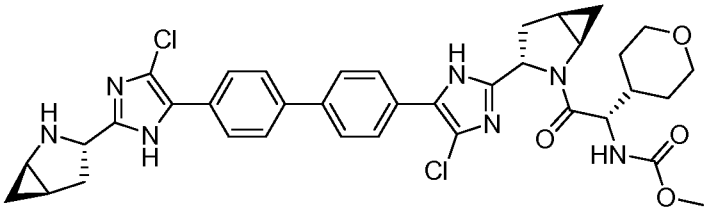
[00399] To a solution of carbamate V9a (1 g, 1.823 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (0.400 g, 1.841 mmol), and N,N-diisopropylethylamine (0.65 mL, 3.72 mmol) in DMF (8 mL) was added HATU (0.770 g, 2.026 mmol), and the reaction mixture was stirred at ~25 °C for 3 h. The volatile component was removed *in vacuo*, and the residue was taken up in 20% MeOH/$CHCl_3$ (250 mL), washed with water (3 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was taken up in $CHCl_3$ (4 mL) and loaded onto a Thomson's silica gel cartridge and eluted with 10% MeOH/EtOAc to afford product V9b as a tan foam (1.15 g). LC (Cond. 1a): R_t = 1.70 min; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}N_7O_6$: 748.38; found: 748.40.

Example V9, Step c



[00400] A solution of V9b (0.9387 g, 1.255 mmol) and NCS (0.335 g, 2.51 mmol) in DMF (13 mL) was heated at 50 °C for 24.5 h. The volatile component was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (200 mL), washed with water (3 x 50 mL), followed by brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (6 mL) and submitted to a silica gel purification (100% ethyl acetate) to afford compound V9c as a yellow solid (720.7 mg). LC (Cond. 1a): R_t = 3.19 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}Cl_2N_7O_6$: 816.30; found: 816.35.

Example V9, Step d



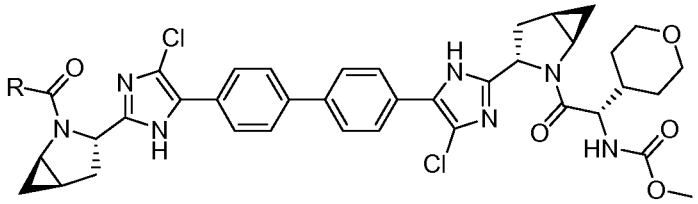
[00401] Pyrroldine V9d was prepared as HCl salt from carbamate V9c according to the procedure described for the synthesis of V1b. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.49-10.38 (m, 1H), 9.84-9.72 (m, 1H), 7.90-7.81 (m, 8H), 7.27 (d, J = 8.6, 0.89H), 6.99 (app br s, 0.11H), 4.98-4.95 (m, 1H), 4.65-4.55 (m, 1H), 4.50-4.46 (m, 1H), 3.90-3.80 (m, 2H), 3.76-3.64 (m, 1H), 3.54 (s, 3H), 3.41-3.32 (m, 1H), 3.32-3.19 (m, 2H), 2.54-2.40 ('m' partially overlapped with solvent signal, 2H), 2.36-2.24 (m, 2H), 2.06-1.95 (m, 1H), 1.94-1.78 (m, 2H), 1.69-1.57 (m, 1H), 1.55-1.40 (m, 2H), 1.39-1.27 (m,1H), 1.17-1.07 (m, 1H), 1.04-0.92 (m, 1H), 0.88-0.78 (m, 1H), 0.76-0.66 (m,1H). LC (Cond. 1a): R_t = 2.66 min; >95% homogeneity index. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{40}Cl_2N_7O_4$: 716.25; found: 716.28.

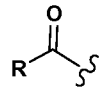
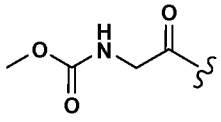
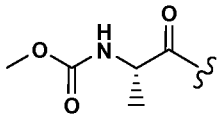
Example V9

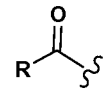
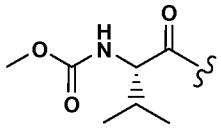
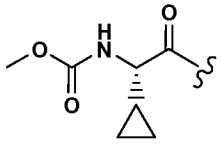
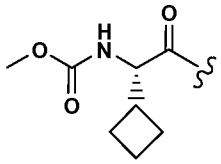
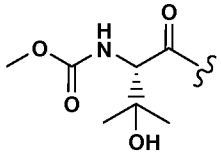
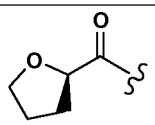
[00402] Example V9 (TFA salt) was prepared from the HCl salt of intermediate V9d and (S)-2-(methoxycarbonylamino)butanoic acid according to the procedure described for the synthesis of Example V1. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.59 (br s, ~2H), 7.87-7.77 (m, 8H), 7.29/7.26 (two partially overlapped 'd', *J* = 8.6/7.8, 1.82H), 6.97 (app br s, 0.18H), 4.97-4.93 (m, 2H), 4.50-4.42 (m, 2H), 3.90-3.81 (m, 2H), 3.72-3.65 (m, 1H), 3.60-3.46 (overlapping m and two s, s are at 3.54 and 3.53, 7H), 3.32-3.18 (m, 2H), 2.38-2.18 (m, 4H), 2.05-1.23 (collection of 'm', 9H), 1.09-0.85 (m, 5H), 0.76-0.59 (m, 2H). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): R_t = 2.66 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}Cl_2N_8O_7$: 859.31; found: 859.43.

Examples V10 to V16

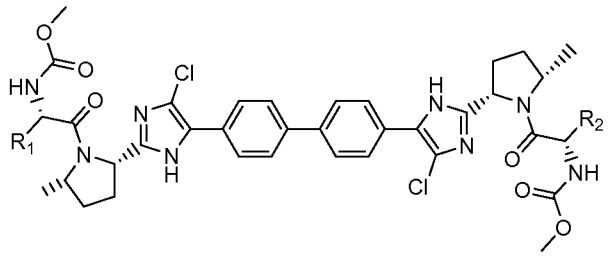
[00403] Examples V10 to V16 (TFA salt) were prepared from the HCl salt of pyrrolidine V9d and appropriate acids according to the procedure described for the preparation of Example V1. Examples V13 toV16 required an additional reverse phase HPLC purification which employed the following condition: Column: Waters SunFire, 30 X 100 mm, S5; Start %B = 10, Final %B = 50; Gradient time = 20 min; Stop time = 20 min; Flow rate = 30 ml/min; Wavelength = 220; Solvent A = 10% Acetonitrile – 90% H_2O – 0.1% TFA; Solvent B = 90% Acetonitrile – 10% H_2O – 0.1% TFA.

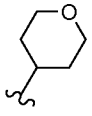


Example		R_t (LC-Cond.); LC (Cond. 2a and 2b): % homogeneity index; MS data
V10		2.59 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}Cl_2N_8O_7$: 831.28; found: 831.31.
V11		2.54 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}Cl_2N_8O_7$: 845.29; found: 845.17.

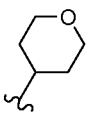
Example		R_t (LC-Cond.); LC (Cond. 2a and 2b): % homogeneity index; MS data
V12		2.69 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}Cl_2N_8O_7$: 873.33; found: 873.27.
V13		2.73 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}Cl_2N_8O_7$: 871.31; found: 871.41.
V14		2.83 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{51}Cl_2N_8O_7$: 885.33; found 885.45.
V15		2.70 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}Cl_2N_8O_8$: 889.32; found 889.44.
V16		2.52 min (Cond. 1a); >95%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}Cl_2N_7O_6$: 814.29; found 814.18.

Examples GW1-1 to GW1-3



$R_1 = R_2 =$ 

Example GW1-1

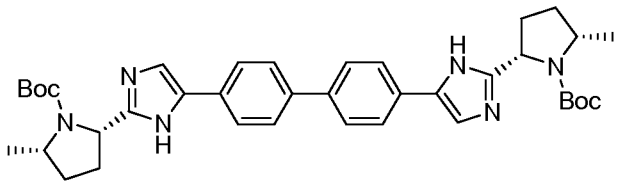
$R_1 =$  $R_2 =$ 

Example GW1-2

$R_1 = R_2 =$ 

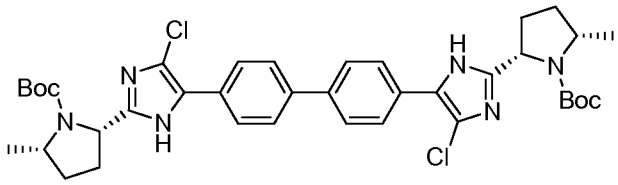
Example GW1-3

Example GW1, Step a



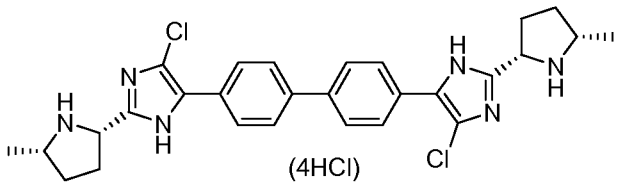
[00404] For the preparation of carbamate GW1a, see U.S. Patent Application 2009/0068140.

Example GW1, Step b



[00405] To a solution of carbamate GQ1a (0.830 g, 1.271 mmol) in DMF (9 mL) was added NCS (0.221 g, 1.653 mmol). The reaction mixture was heated at 50 °C for 16 hr. More NCS (0.1 g, 0.75 mmol) was added and heating was continued for another 4 hr. It was allowed to cool to ambient temperature and partitioned between DCM and water (20 mL each). The aqueous layer was extracted with DCM (20 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude material was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salts of GW1b as light yellow foam (0.25g). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.82 (app s, 8H), 4.95-4.85 ('m' partially overlapped with HOD signal, 2H), 4.04 (m, 2H), 2.36-2.14 (m, 6H), 1.77 (m, 2H), 1.50-1.20 (overlap of 'br s' and 'd', 24H). LC (Cond. Ia): RT = 3.0 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}Cl_2N_6O_4$: 721.30; found 721.32.

Example GW1, Step c



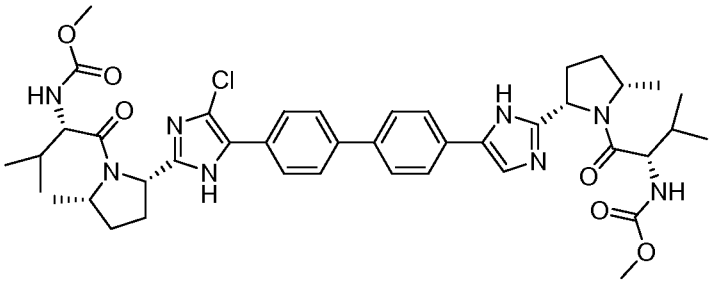
(4HCl)

[00406] 4N HCl in dioxane (10 mL) was added to carbamate GW1b (0.29 g, 0.306 mmol) and the reaction mixture was stirred at room temperature for 4 hrs. Solvent was removed and dried under vacuum overnight to give the HCl salt of product GW1c as brown solid (0.21g). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.85 (d, *J* = 8.6, 4H), 7.80 (d, *J* = 8.8, 4H), 4.95-4.85 (m, 2H), 3.89-3.80 (m, 2H), 2.58-2.31 (m, 6H), 2.01-1.91 (m, 2H), 1.50 (d, 6.5 Hz, 6H). LC (Cond. 1a): RT = 3.0 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{31}Cl_2N_6$: 521.20; found 521.20.

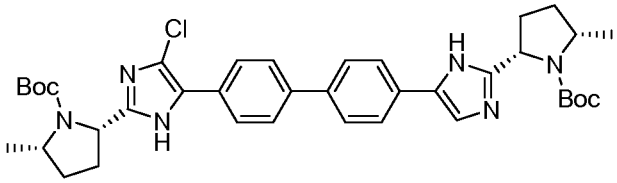
Examples GW1-1 to GW1-3

[00407] To a solution of the HCl salt of GW1c (150 mg, 0.225 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (57.6 mg, 0.265 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (48.0 mg, 0.274 mmol) in DMF (10 mL) were added DIEA (0.236 mL, 1.349 mmol) and HATU (176 mg, 0.463 mmol), and the mixture was stirred at room temperature for 1 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to isolate the three products as TFA salts. Example GW1-1 (light yellow foam, 25 mg) was contaminated with unidentified impurity. ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 8.05-7.93 (m, 1.54H), 7.87-7.56 (m, 6.46H), 5.42 (br d, *J* = 6.6, 0.68H), 4.97 (m, 1.32H), 4.76-4.69 (m, 1.2H), 4.31-4.14 (m, 2.8H), 3.98-3.84 (m, 4H), 3.68/3.67/3.63 (three 's', 6H), 3.40-3.21 ('m' partially overlapped with solvent signal, 4H), 2.72 (m, 0.7H), 2.45-1.14 (overlapped many 'm' and two 'd', 'd' at 1.51 and 1.18 with *J* = 6.5 and 6.3, respectively; 23.3H). LC (Cond. 2a and 2b): >91.8% homogeneity index. LC (Cond. 1c): RT = 6.22 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}Cl_2N_8O_8$: 919.37; found 919.9. Example GW1-2 (light yellow foam, 39 mg); LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): RT = 2.97 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}Cl_2N_8O_7$: 877.36; found 877.35. Example GW1-3 (light yellow foam, 22 mg), LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. 1a): RT = 3.07 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; found 835.34.

Example GW2

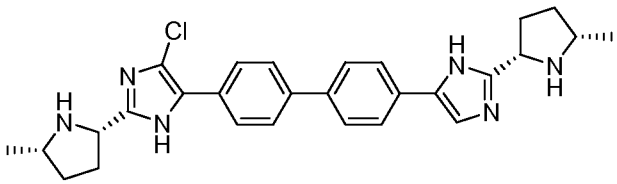


Example GW2, Step a



[00408] To a solution of carbamate GW1a (0.830 g, 1.271 mmol) in DMF (9 mL) was added NCS (0.221 g, 1.653 mmol). The reaction mixture was heated at 50 °C for 16 hr. Additional NCS (0.1g, 0.75 mmol) was added and heating was continued at 50 °C for an additional 4 hr. The mixture was partitioned between DCM and water (20 mL each). The aqueous phase was extracted with DCM (20 mL), and the combined phase was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve carbamate GW2a as light yellow foam (0.03g). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.76-7.64 (m, 8H), 7.34 (s, 1H), 5.10-4.65 (overlapping with HOD signal, m, 2H), 3.99 (m, 2H), 2.31-2.01 (m, 6H), 1.78-1.76 (m, 2H), 1.55-1.15 (app br m, 24H). LC (Cond. 1a): RT = 2.55 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}ClN_6O_4$: 687.34; found 687.39.

Example GW2, Step b



[00409] 4N HCl in dioxane (10 mL) was added to carbamate GW2a (0.19 g, 0.208 mmol) and it was stirred at room temperature for 4 hr. Solvent was removed and it was dried under vacuum overnight to afford the HCl salt of pyrrolidine GW2b as brown solid

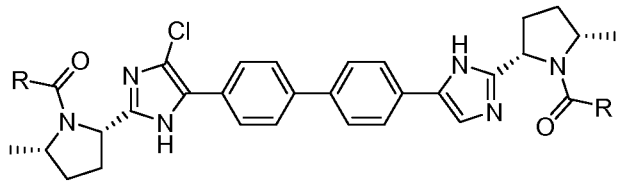
(0.16g). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 8.11 (s, 1H), 7.95 (d, *J* = 8.5, 2H), 7.87 (appears 'd', 4H), 7.82 (d, *J* = 8.8, 2H), 5.22 (m, 1H), 4.92 – 4.83 (over lapping with HOD signal, m, 1H), 3.99 (m, 1H), 3.84 (m, 1H), 2.78-2.62 (m, 2H), 2.57-2.31 (m, 4H), 2.12-1.91 (m, 2H), 1.55 (d, *J* = 6.8, 3H), 1.50 (d, *J*= 6.8, 3H). LC (Cond. Ia): RT = 1.74 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{32}ClN_6$: 487.24; found 487.21.

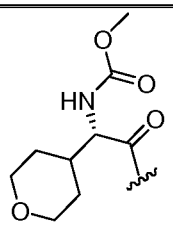
Example GW2

[00410] To a solution of the HCl salt of pyrrolidine GW2b (80 mg, 0.126 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (48.7 mg, 0.278 mmol) in DMF (3 mL), DIEA (0.132 mL, 0.758 mmol) and HATU (99 mg, 0.260 mmol) were added and the mixture was stirred at room temperature for 1 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salts of GW2 (light yellow foam; 50 mg). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 8.00-7.75 (m, 9H), 5.71 (app br m, 0.2H), 5.40 (d, *J* = 6.3, 0.45 H), 5.15-5.11 (m, 0.87H), 5.00-4.96 (m, 0.92H), 4.81-4.68 (m, 1.56H), 4.26-4.03 (m, 2H), 3.71/3.70/3.64/3.63 (four 's', 6H), 2.77-1.87 (m, 9.24H), 1.65-1.48 (overlapped 'm' and 'd', 4.66 H), 1.28 (d, *J* = 0.62H), 1.17 (d, *J* = 6.3H, 1.23H), 1.06-0.82 (m, 12.15H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. 1a): RT = 2.46 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{54}ClN_8O_5$: 801.39; found 801.41.

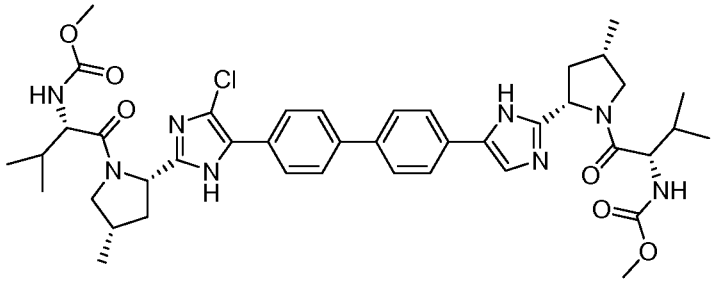
Example GW2-1

[00411] Example GW2-1 (TFA salt) was prepared from pyrrolidine GW2b and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid according to the procedure described for the preparation of Example GW2.

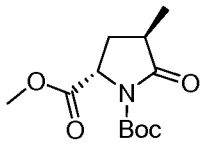


Example		RT (LC-Cond.); % homogeneity index; MS data
GW2-1		2.23 min (Cond. 1a); >98%; LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{58}ClN_8O_8$: 885.41; found 885.37

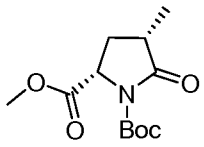
Example GW3



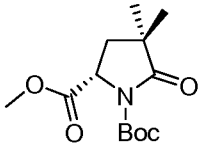
Example GW3, Step a



GW3a-1



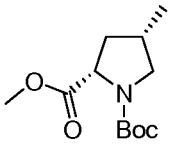
GW3a-2



GW3a-3

[00412] The above three esters were prepared from (*S*)-1-*tert*-butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate according to the procedure described in *Tetrahedron Letters*, 3203-3205 (2003).

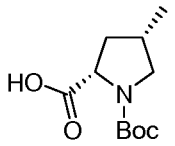
Example GW3, Step b



[00413] Borane-methyl sulfide complex (5.44 mL, 10.88 mmol) was added to a solution of ester GW3a-2 (1.4 g, 5.44 mmol) in THF (25 mL), and the reaction mixture

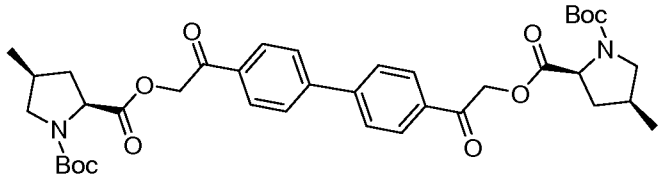
was heated at 40 °C for 7 hr. The volatile component was removed *in vacuo* and the residue was partitioned between EtOAc and water (50 mL each). The aqueous layer was extracted with EtOAc (30 mL), and the combined organic phase was dried with Na_2SO_4, and concentrated *in vacuo*. The resultant colorless oil was purified with a flash chromatography (0-50% EtOAc/Hexane) to afford ester GW3b as a colorless oil (0.77 g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.29-4.18 (m, 1H), 3.78-3.66 (m, 4H), 2.99 (app t, *J* = 10.1, 1H), 2.43-2.97 (m, 1H), 2.43-2.37 (m, 1H), 2.30-2.18 (m, 1H), 1.60-1.52 (m, 1H), 1.47/1.42 (two 's', 9H), 1.08-1.05 (m, 3H).

Example GW3, Step c



[00414] To a solution of ester GW3b (1.69 g, 6.95 mmol) in ethanol (10 mL) was added solution of LiOH (0.250 g, 10.42 mmol) in water (5.00 mL), and the reaction mixture was stirred at room temperature for 5 hr. The organic solvent was evaporated *in vacuo* and the residue was diluted with water (10 mL) and washed with ether (10 mL). It was chilled in ice-water bath, and acidified to a pH range of ~2 with 1N HCl. It was then extracted with EtOAc (20 mL, 3x). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford acid GW3c as a colorless oil, which became a white solid upon extended exposure to high vacuum (1.38g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.39-4.22 (m, 1H), 3.80-3.69 (m, 0.91H), 3.59-3.35 (m, 0.18H), 3.03-2.89 (m, 0.91H), 2.51-2.22 (m, 2H), 1.98-1.91 (m, 0.71H), 1.68-1.60 (0.29H), 1.50/1.44 (two 's', 9H), 1.09 (app m, 3H).

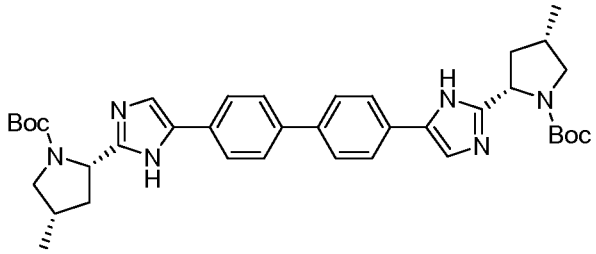
Example GW3, Step d



[00415] To a suspension of GW3c (1.83 g, 7.98 mmol) and 1,1′-(biphenyl-4,4′-diyl)bis(2-bromoethanone) (1.581 g, 3.99 mmol) in CH_3CN (30 mL) was added DIEA

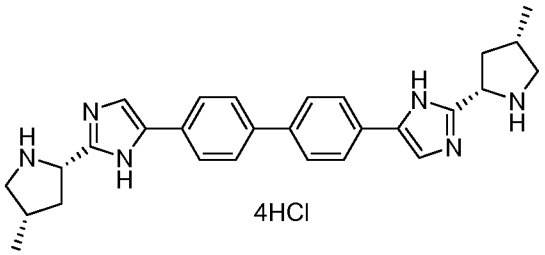
(1.436 mL, 8.22 mmol), and the mixture was stirred at room temperature for 4 hr. Solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and water (50 mL each). The organic layer was washed with sat. $NaHCO_3$ (20 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afford diester GW3d as light yellow solid (2.67g), which was used as is for the next step.

Example GW3, Step e



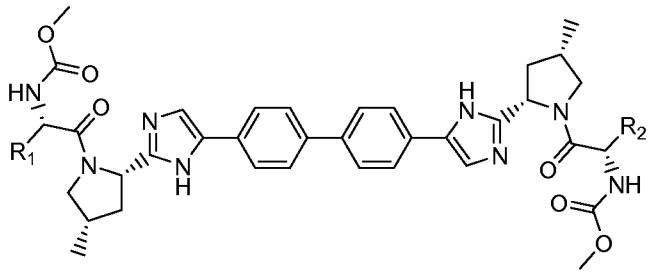
[00416] To a solution of diketoester GW3d (2.67 g, 3.85 mmol) in xylenes (30 mL) was added ammonium acetate (2.97 g, 38.5 mmol), and the mixture was heated at 140 °C for 6 hr in a sealed tube. The volatile component was removed *in vacuo* and the residue was partitioned between DCM (50 mL) and water (50 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The resulting crude material was purified with a flash chromatography (50-100% EtOAc/Hexane, 100% EtOAc-10% MeOH/EtOAc)) to afford imidazole GW3e as orange solid (1.3g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21-11.87 (three br s, 2H), 7.82-7.51 (m, 9.2H), 7.30 (m, 0.6H), 6.88-6.81 (m, 0.2H), 4.9-4.67 (m, 1.81H), 3.98-3.93 (m, 0.19H), 3.77-3.54 (m, 2H), 3.07-2.76 (m, 2H), 2.43-2.04 (m, 4H), 1.80-1.56 (m, 2H), 1.41-1.33 (m, 8H), 1.10-1.04 (m, 16H). LC-MS (Cond. 1a): RT = 2.09 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; found 653.51.

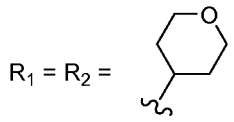
Example GW3, Step f



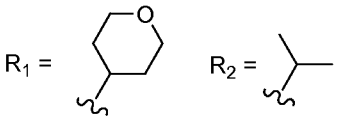
[00417] 4N HCl in dioxane (12.10 mL, 48.4 mmol) was added to carbamate GW3e (1.3 g, 1.99 mmol) and the mixture was stirred at room temperature for 5 hr. The volatile component was removed *in vacuo*, and the product was dried under vacuum overnight to afford HCl salt of pyrrolidine GW3f as a yellow solid (1.14g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.32 (app br s, 2H), 9.79 (app br s, 2H), 8.13 (s, 2H), 8.02 (d, *J*=8.3, 4H), 7.99 (d, *J*=8.3, 4H), 5.01 (br m, 2H), 3.47 (br m, 2H), 3.05 (br m, 2H), 2.62 (m, 2H), 2.45 (m, 2H), 2.21 (m, 2H), 1.13 (d, *J* = 6.3, 6H). LC-MS (Cond. 1a): RT = 2.09 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{33}N_6$: 453.28; found 453.17.

Example GW3, Step g

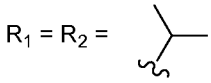




(GW3g-1)



(GW3g-2)



(GW3g-3)

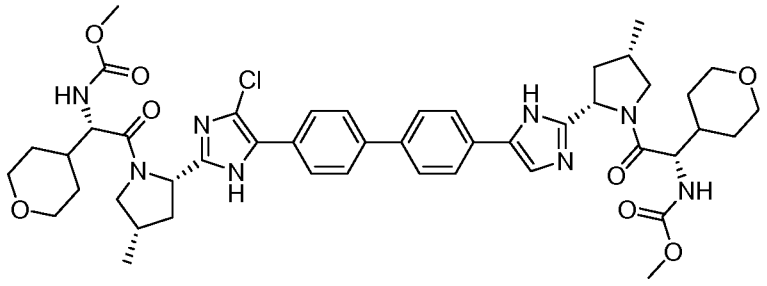
[00418] To a suspension of the HCl salt of pyrrolidine GW3f (1.14 g, 1.905 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (0.488 g, 2.248 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.407 g, 2.324 mmol) in DMF (15 mL) was added DIEA (1.996 mL, 11.43 mmol). Total dissolution was effected with the help of sonication, and then HATU (1.478 g, 3.89 mmol) was added, and the reaction mixture was stirred at room temperature for 2 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to afford TFA salts of three products: GW3g-1 (0.28g), GW3g-2 (0.64g) and GW3g-3 (0.36g) as light yellow foam. Product GW3g-3: ^{1}H NMR (DMSO, δ = 2.5 ppm, 400 MHz): 14.74 (app br s, not integratable), 8.16 (s, 2H), 7.97 (d, *J*=8.6, 4H), 7.88 (d, *J*=8.3, 4H), 7.29 (d, *J*=8.0, < 2H), 5.23 (br m, 0.1H), 5.07 (dd, *J* = 10.6, 7, 1.9H), 4.18 (m, 2H), 4.09 (m, 2H), 3.53 (s, 6H), 3.39 (m, 2H), 2.56-2.35 ('m'

partially overlapped with solvent signal, 2H), 1.95 (m, 2H), 1.82 (m, 2H), 1.13 (d, *J*=6.3, 6H), 0.79 (d, *J*=6.5, 6H), 0.76 (d, *J*=6.5, 6H) [Note: the last three integrations include minor rotamers with signals in the 1.1-0.85 ppm region that were not peak-picked]. LC-MS (Cond. 1a): RT = 1.79 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; found 767.30. Product GW3g-1, LC-MS (Cond. Ia): RT = 1.62 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{46}H_{59}N_8O_8$: 851.45; found 851.33. Product GW3g-2, LC-MS (Cond. 1a): RT = 1.70 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}N_8O_7$: 809.44; found 809.30.

Example GW3

[00419] To a solution of GW3g-3/2TFA (160mg, 0.174 mmol) in DMF (2 mL) was added NCS (30.6 mg, 0.229 mmol). The mixture was heated to 50 °C for 5.5 hr. The residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salts of GW3 as light yellow foam (40 mg). [Note: for analogous cases the chlorination was conducted on a starting material that was in a free base form.] ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.88 (s, 1H), 7.84-7.76 (m, 8H), 5.19 (dd, *J* = 11.1, 7.1, 1H), 4.98 (dd, *J* = 10.4, 7.3, 1H), 4.32 (m, 1H), 4.24-4.17 (m, 3H), 3.63 (s, 3H), 3.62 (s, 3H), 3.40-3.33 (m, 2H), 2.65 (m, 1H), 2.50 (m, 2H), 2.37 (m, 1H), 1.99 (m, 2H), 1.82 (m, 2H), 1.22 (d, *J*=6.3, 2.85H), 1.18 (d, *J*=6.3, 2.85H), 1.09 (m, 0.3H), 0.92-0.85 (m, 12H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 2.32 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{54}ClN_8O_6$: 801.39; found 801.25.

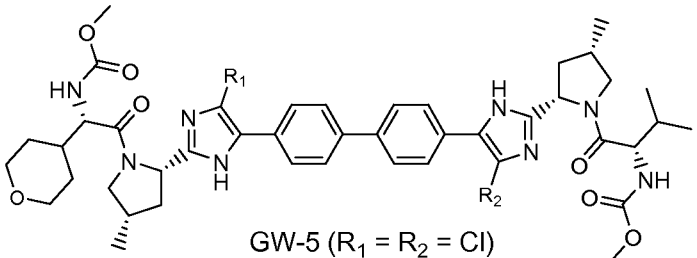
Example GW4



[00420] Example GW4 (TFA salt) was prepared from GW3g-1 according to the procedure described for the preparation of Example GW3. LC (Cond. 2a and 2b): >95%

homogeneity index. LC-MS (Cond. Ia): RT = 2.17 min (Cond. 1a). LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{58}ClN_8O_8$: 885.41; found 885.26.

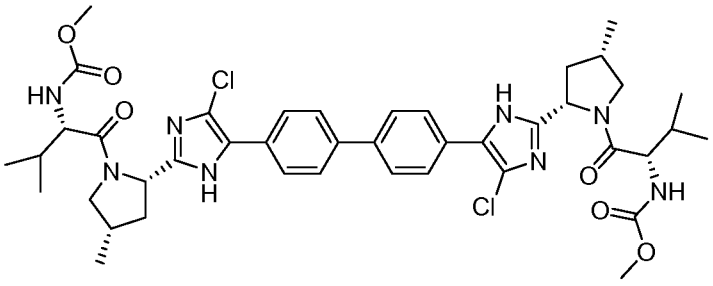
Examples GW5 to GW7



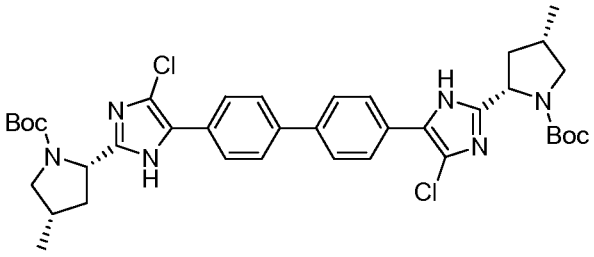
[00421] To a solution of GW3g-2 (565mg, 0.588 mmol) in DMF (2 mL) was added NCS (0.021 g, 0.161 mmol), and the reaction mixture was heated at 50 °C for 17 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to afford two fractions (one is GW5 and the second one is mixture of GW6 and GW7). The fractions were dried by *in vacuo* and retrieved as light yellow solid. Both fractions were dissolved separately in methanol and submitted to a reverse phase HPLC purification (ACN/TFA/Water, Water-SunFire 30X100 mm S5) to retrieve the TFA salts of Example GW5, GW6 and GW7. Example GW5: ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.74 (m, 8H), 5.02 (m, 2H), 4.29-4.18 (m, 4H), 3.90 (m, 2H), 3.63 (s, 6H), 3.41-3.33 (m, 4H), 2.52 (m, 2H), 2.39 (br m, 2H), 2.01-1.79 (m, 4H), 1.58-1.27 (m, 4H), 1.18 (d, *J*=6.5, 5.63H), 1.09 (m, 0.37H), 0.93 (d, *J*=6.8, 3H), 0.88 (d, *J*=6.5, 3H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. 1a): RT = 2.81 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}Cl_2N_8O_7$: 877.36; found 877.30. Example GW6: ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.86 (s, 1H), 7.82-7.73 (m, 8H), 5.19 (dd, *J* = 11, 7, 1H), 4.98 (dd, *J* = 10.4, 7.3, 1H), 4.33-4.19 (m, 4H), 3.90 (m, 2H), 3.67 (m, 0.35H), 3.63/3.62 (two overlapped 's', 5.65H), 3.41-3.31 (m, 4H), 2.65 (m, 1H), 2.49 (m, 2H), 2.38 (m, 1H), 2.00-1.79 (m, 4H), 1.57-1.27 (m, 4H), 1.22/1.18 (two overlapping 'd', *J* = 6.5/6.3, respectively, 5.69H), 1.09 (m, 0.31H), 0.90/0.86 (two overlapping 'd', *J* = 6.8/6.8, 6H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 2.25 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{56}ClN_8O_7$: 843.40; found 843.24. Example GW7: ^{1}H NMR (MeOD, δ =

3.30 ppm, 400 MHz): 7.87-7.75 (m, 9H), 5.19 (dd, *J*= 11. 7.0, 1H), 4.99 (dd, *J* = 10.3, 7.3, 1H), 4.38-4.17 (m, 4H), 3.90 (m, 2H), 3.64/3.62 (two 's', 6H), 3.41-3.26 ('m' partially overlapped with solvent signal, 4H), 2.64 (m, 1H), 2.50 (m, 2H), 2.37 (m, 1H), 2.03-1.79 (m, 4H), 1.60-1.08 (m, 10H), 0.92 (d, *J*=6.8, 3H), 0.86 (d, *J*=6.8, 3H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. 1a): RT = 2.24 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{56}ClN_8O_7$: 843.40; found 843.24.

Example GW8

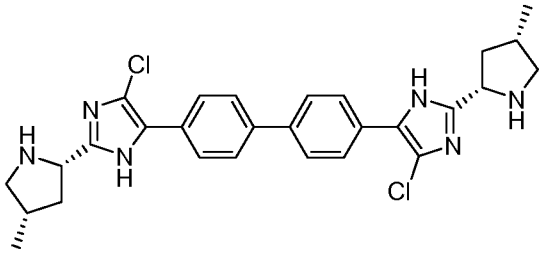


Example GW8, Step a



[00422] To a solution of GW3e (0.360 g, 0.551 mmol) in DMF (9 mL) was added NCS (0.096 g, 0.717 mmol), and the reaction mixture was heated at 50 °C for 15 hr. The residue was diluted with MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salt of carbamate GW8a as light yellow foam (20 mg). TFA salts of GW3e (60 mg) and the mono-chloro analog (70 mg) were also isolated. Carbamate GW8a: ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.83 (app s, 8H), 4.95-4.79 ('m' partially overlapped with HOD signal, 2H), 3.85-3.75 (m, 2H), 3.14 (m, 2H), 2.58-2.48 (m, 2H), 2.44-2.30 (m, 2H), 1.80-1.71 (m, 2H), 1.43 (s, 6H), 1.23 (s, 12H), 1.14/1.12 (two overlapping 's', 6H). LC-MS (Cond. Ia): RT = 2.98 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}ClN_6O_4$: 721.30; found 721.39.

Example GW8, Step b

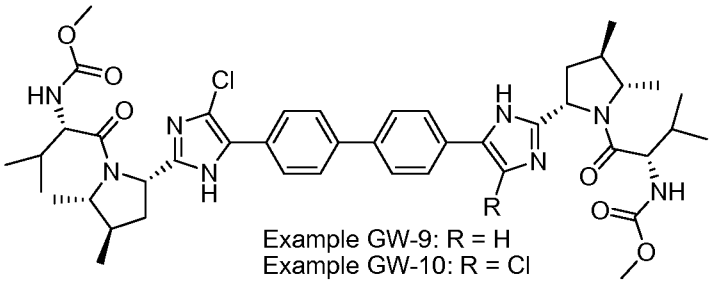


[00423] 4N HCl in dioxane (3 mL) was added to the TFA salt of GW8a (55 mg, 0.063 mmol), and the mixture was stirred at room temperature for 5 hr. Solvent was removed *in vacuo* and the residue was dried under vacuum overnight to afford the HCl salt of pyrrolidine GW8b as a brown solid (50mg). LC-MS (Cond. Ia): RT = 2.20 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{31}Cl_2N_6$: 521.20; found 521.20.

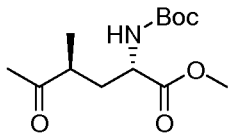
Example GW8

[00424] To a suspension of the HCl salt of GW8b (50 mg, 0.075 mmol) in DMF (3 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.9 mg, 0.165 mmol), DIEA (0.079 mL, 0.450 mmol), and HATU (58.7 mg, 0.154 mmol), and the mixture was stirred at room temperature for 2 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to retrieve the TFA salts of GW8 (light yellow foam; 40 mg). ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.80-7.75 (m, 8H), 5.01 (dd, J = 10.4, 7.4, 2H), 4.26-4.17 (m, 4H), 3.63 (s, 6H), 3.38-3.33 (m, 2H), 2.52-2.49 (m, 2H), 2.45-2.33 (m, 2H), 2.03-1.95 (m, 2H), 1.87-1.79 (m, 2H), 1.19 (d, J=6.3, 6H), 0.92 (d, J=6.8, 6H), 0.87 (d, J=6.8, 6H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 2.89 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; found 835.41.

Examples GW9 and GW10

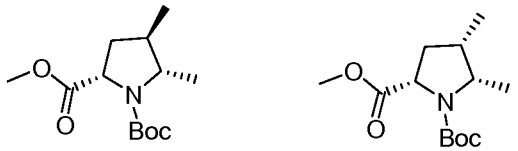


Example GW9, Step a



[00425] To a solution of GW3a-2 (1.31 g, 5.09 mmol) in THF (25 mL) was added methylmagnesium bromide (2.037 mL, 6.11 mmol) dropwise at -40 °C (dry ice/acetone bath). It was stirred at the same temperature for 2 hr, and then the bath was removed and stirring was continued for an additional 1 hr. Acetic acid (1 mL), water (10 mL) and ether (50 mL) were added, the mixture was shaken and the organic layer was separated. The organic layer was washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The resultant crude material was purified with a flash chromatography (5-95% EtOAc/Hexane) to afford ester GW9a as colorless oil (0.6g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.97 (br d, J = 8.3, 1H), 4.29 (m, 1H), 3.74/3.73 (overlapping 's', 3H), 2.66 (m, 1H), 2.27-2.22 (m, 0.21H), 2.17 (s, 2.58H), 2.10-2.02 (m, 1.22H), 1.80-1.1.74 (m, 1H), 1.43/1.40 (overlapping 's', 9H), 1.16 (d, J=7.1, 2.6H), 1.05(d, J=6.8, 0.4H).

Example GW9, Step b

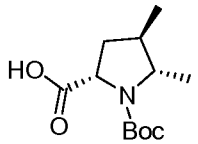


[00426] To a solution of ketone GW9a (0.6 g, 2.195 mmol) in DCM (15 mL) was added TFA (0.846 mL, 10.98 mmol), and the mixture was stirred at room temperature for 7 hr. The volatile component was removed *in vacuo*, and dried under vacuum overnight to afford a light yellow oil (0.63g).

[00427] A solution of the above crude product (0.5g, 1.8 mmol) in methanol (20 mL) was added to a 500 mL Parr shaker bottle containing Pd/C (0.025 g, 0.234 mmol). After evacuation and refilling with nitrogen was conducted (3x), the mixture was shaken under 60 psi for 24 hr. The reaction mixture was filtered through a filter paper and the volatile component was removed *in vacuo* to afford a light yellow oil (0.41g).

[00428] To a solution of the above crude product (0.48g, 1.77 mmol) in CH_2Cl_2 (7 mL) was added DMAP (10.81 mg, 0.088 mmol), triethylamine (0.740 mL, 5.31 mmol). Di-*tert*-butyl dicarbonate (0.386g, 1.77 mmol) was added in portions over 15 min and the mixture was stirred at room temperature for 18 hr. After the volatile component was removed *in vacuo*, the crude material was purified with a flash chromatography (0-22% EtOAc/Hexane) to afford two major products. The first elute was GW9b-1 (0.54g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.41/4.30 (br m, 1H), 3.74 (s, 3H), 3.48/3.33 (br m, 1H), 2.37-2.22 (m, 0.2H), 2.10-2.04 (m, 0.9H), 1.98-1.19 (m, 0.9H), 1.79 (m, 1H), 1.46-1.32 (m, 12H), 1.05/1.01/0.97 (three overlapping 'd', J = 6.8/6.6/6.3, respectively, 3H). The second elute was GW9b-2 contaminated with unidentified impurity (0.48 g). Clean fractions of GW9b-2 was used to acquire the following spectral data: ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.23-4.12 (two overlapping 'dd', 1H), 4.00-3.85 (two overlapping 'm', 1H), 3.72/3.71 (overlapping 's', 3H), 2.34-2.20 (m, 2H), 1.69-1.55 (1H), 1.45/1.39 (overlapping 's', 9H), 1.13-1.01 (m, 3.13H), 0.97 (d, J = 6.3, 2.87H).

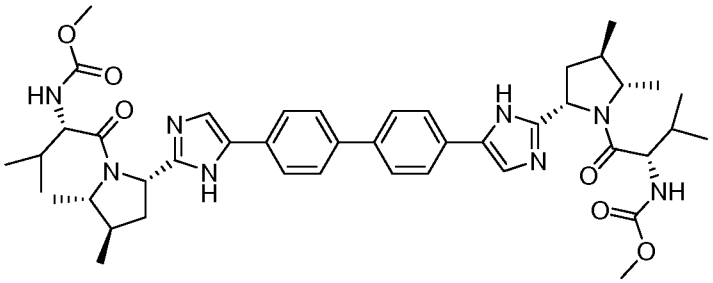
Example GW9, Step c



[00429] To a solution of GW9b-1 (3.73 g, 14.50 mmol) in ethanol (40 mL) was added solution of LiOH (0.417 g, 17.39 mmol) in water (20.00 mL), and the mixture was stirred at room temperature for 6 hr. More LiOH (0.1g, 4.3 mmol) was added, and stirring was continued for an additional 2 hr. Most of the organic component was evaporated, and the remaining portion was washed with ether (20 mL). The aqueous layer was chilled with ice-water bath, acidified with 1N HCl to a pH of 2-3, extracted with EtOAc (50 mL, 4x), dried with Na_2SO_4, and concentrated to afford a colorless oil, which became a white solid upon exposure to high vacuum (3.43g). The solid was dissolved in a minimum amount of

EtOAc with the help of heating gun that brought it to a refluxing condition. After cooling down to room temperature, 5 drops of hexane were added and allowed to stand at ambient temperature overnight to afford acid GW9c as white needles, which was filtered and washed with hexane, dried under vacuum (2.02g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.40 (app dd, *J*=8.3, 2.8, 1H), 3.30 (br m, 1H), 2.50 (br m, 1H), 2.01-1.93 (m, 1H), 1.68-1.59 (m, 1H), 1.52 (s, 9H), 1.29 (d, *J*=6.0, 3H), 1.07 (d, *J*=6.8, 3H).

Example GW9, Step d



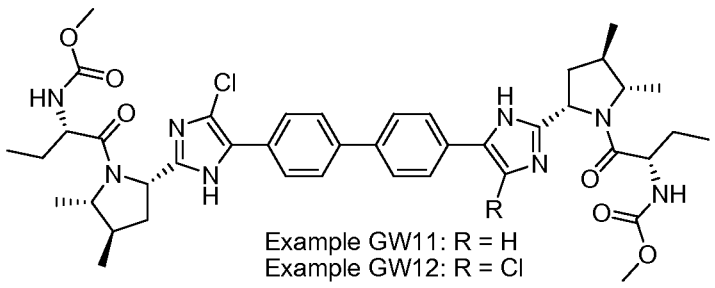
[00430] Compound GW9d (TFA salt; light yellow foam) was prepared from acid GW9c according to the procedure described for the preparation of precursors GW3g from acid GW3c with the exception that (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid was employed for the final step. ^{1}H NMR (MeOD, δ = 3.30 ppm, 400 MHz): 7.97-7.96 (m, 2H), 7.88-7.82 (m, 8H), 5.70 (br d, *J* = 6.7, 0.6H), 5.29 (dd, *J* = 10.3, 1.2H), 5.19-5.14 (m, 0.2H), ~4.90 (overlapped with HOD signal, 1H), 4.38 (m, 1H), 4.12-4.06 (m, 2H), 3.71/3.67/3.64 (overlapping 's', 6H), 2.73-2.68 (m, 0.6H), 2.53-2.45 (m, 1.4H), 2.35-2.18 (m, 2.5H), 2.07-1.82 (m, 3.5H), 1.53 (d, *J* = 6.8, 3.6H), 1.40 (d, *J* = 7.1, 0.5H), 1.30 (d, *J* = 7.1, 1.9H), 1.17-0.83 (collection of overlapping 'd', 18H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 2.07 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{59}N_8O_6$: 795.46; found 795.44.

Examples GW9 and GW10

[00431] To a solution of GW9d (TFA salt; 310 mg, 0.328 mmol) in DMF (6 mL) was added NCS (62.5 mg, 0.468 mmol), and the mixture was heated at 50 °C for 9 hr. Most of the volatile component was removed *in vacuo* and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA; column: PHENOMENEX® Luna, 30X100 mm S10 Axia) to separate the mono- and di-chloro

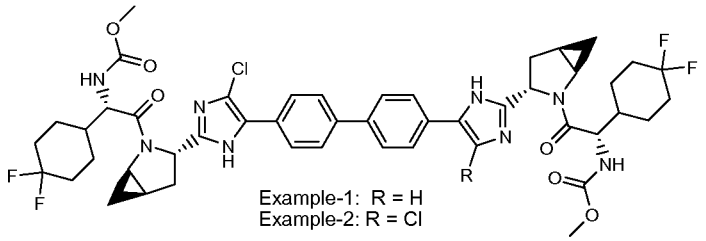
products. The mono-chlorinated product was further purified with a different reverse phase HPLC condition (ACN/TFA/Water, Water-SunFire 30X100 mm S5). Example GW9 (light yellow foam; 36 mg) and Example GW10 (light yellow foam; 60 mg) were retrieved as TFA salts. Example GW9: ^{1}H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 12.71-12.64 (br m, 1H), 8.10 (br s, 1H), 7.95-7.83 (m, 8H), 7.64-7.58 (m, 1.4H), 7.51 (d, *J*=8.6, 0.6H), 5.56 (m, 0.22H), 5.33 (m, 0.33H), 5.16 (m, 0.78H), 5.04 (m, 0.67H), 4.27-4.11 (m, 2H), 3.93-3.86 ('m' overlapped with H_2O signal, 2H), 3.56-3.53 (m, 6H), 2.62-1.64 (collection of 'm', 8H), 1.50-0.75 (collection of 'd', 24H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 2.66 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{58}ClN_8O_6$: 829.42; found 829.44. Example GW10: ^{1}H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 12.7 (br m, 2H), 8.00-7.80 (m, 8H), 7.63 (m, 0.76H), 7.51 (d, *J*=8.6, 1.09H), 7.08 (m, 0.09H), 6.57 (m, 0.05H), 5.33 (d, *J*=6.3, 0.74 H), 5.05 (app t, 1.26H), 4.25-4.12 (m, 2H), 3.90-3.85 ('m' overlapped with H_2O signal, 2H), 3.58-3.49 (m, 6H), 2.59-2.55 (m, 0.5H), 2.33-2.13 (m, 2.7H), 1.98-1.88 (m, 4.05H), 1.71-1.63 (m, 0.75H), 1.43 (d, *J*=6.6, 3.7H), 1.18 (d, *J*=6.3, 2.05H), 1.05-0.76 (collection of 'd', 18.25H). LC (Cond. 2a and 2b): >95% homogeneity index. LC-MS (Cond. Ia): RT = 3.29 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}Cl_2N_8O_6$: 863.38; found 863.38.

Examples GW11 and GW12

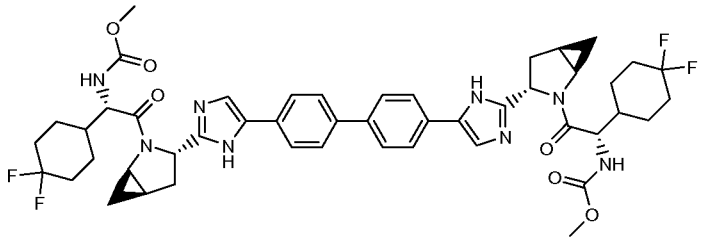


[00432] Examples GW11 and GW12 were prepared according to the procedure described for the preparation of Examples GW9 and GW10 with the exception that (S)-2-(methoxycarbonylamino)butanoic acid was used in place of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid. Example GW11(TFA salt): LC-MS (Cond. Ia): RT = 2.57 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{54}ClN_8O_6$: 801.39; found 801.38. Example GW12 (TFA salt): LC-MS (Cond. Ia): RT = 3.24 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; found 835.31.

Examples OL1 and OL2



Example OL1, Step a

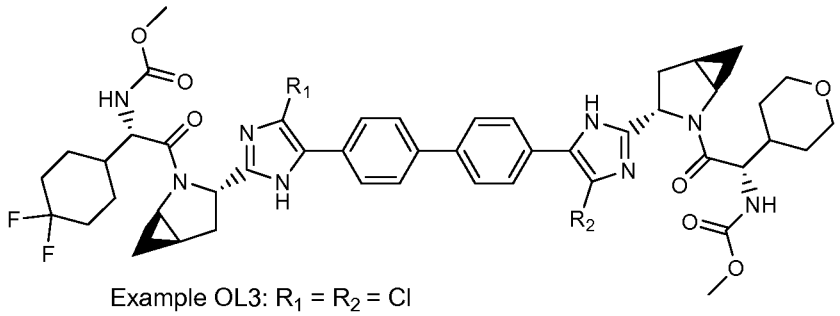


[00433] Pyrrolidine 1e/4HCl (455 mg, 0.766 mmol), (S)-2-(4,4-difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid (385 mg, 1.532 mmol), HATU (612 mg, 1.609 mmol) and DIEA (0.803 mL, 4.60 mmol) were combined in DMF (30 mL) and the resulting yellow solution was stirred at ambient temperature for 3 h. Solvent was removed under reduced pressure and the residue was re-dissolved in methanol and purified by preparatory HPLC.(Solvent A: 10% Acetonitrile / 90% water / 10 mM NH_4OAc; Solvent B: 90% Acetonitrile / 10% water / 10 mM NH_4OAc; Column: SunFire Prep MS C18 30 x 150mm S10; Wavelength: 220nM; Flow rate: 40 ml/min; Gradient: 10% B to 75% B over 30 min with a 30 min hold time). An off-white solid corresponding to product OL1a (0.37 g, 0.396 mmol) was recovered. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.67 - 12.26 (2 H, m), 7.80 (4 H, d, *J*=7.93 Hz), 7.67 - 7.76 (1 H, m), 7.65 (4 H, d, *J*=8.24 Hz), 7.54 (2 H, s), 7.23 - 7.35 (2 H, m), 5.07 (2 H, dd, *J*=8.24, 3.66 Hz), 4.54 (2 H, t, *J*=7.93 Hz), 3.62 (2 H, d, *J*=4.27 Hz), 3.55 (6 H, s), 2.36 (2 H, t, *J*=10.99 Hz), 2.20 - 2.30 (2 H, m), 2.01 (4 H, br. s.), 1.57 - 1.85 (9 H, m), 1.19 - 1.53 (6 H, m), 0.92 - 1.08 (2 H, m), 0.71 (2 H, br. s.). LC (Cond. OL3): R_t = 0.79 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}F_4N_8O_6$: 915.42; found: 915.8. HPLC purity assessment (Cond. OL4a): R_t = 23.12 min, homogeneity index = 98.4 %.

Examples OL1 and OL2

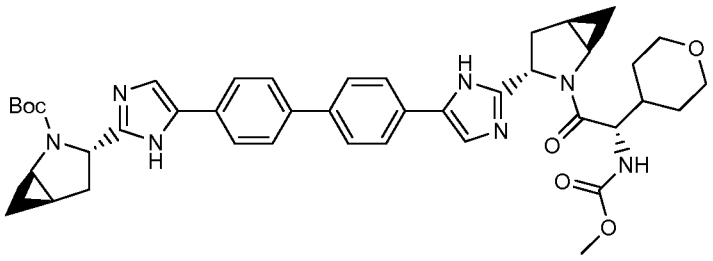
[00434] NCS (6.83 mg, 0.051 mmol) was added to a solution of amide OL1a (39 mg, 0.043 mmol) in DMF (2 mL) and the resulting mixture was heated to 50 °C for 5 h. The reaction mixture was then purified by preparatory HPLC. Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: SunFire Prep MS C18 30 x 100mm 5u; Wavelength: 220nM; Flow rate: 40 ml/min; Gradient: 0% B to 75% B over 30 min with a 2 min hold time. After concentration of the fractions the TFA salts of Example OL1 (15 mg) and Example OL2 (16 mg) were isolated. Example OL1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.11 (1 H, s), 7.74 - 8.00 (8 H, m), 7.40 (1 H, d, *J*=8.55 Hz), 7.28 (1 H, d, *J*=8.24 Hz), 4.91 - 5.05 (2 H, m), 4.48 - 4.59 (2 H, m), 3.74 - 3.87 (2 H, m), 3.62 - 3.71 (1 H, m), 3.55 (3 H, s), 3.54 (3 H, s), 2.19 - 2.43 (6 H, m), 1.66 - 2.07 (19 H, m), 1.56 (1 H, d, *J*=10.38 Hz), 1.26 - 1.48 (5 H, m), 0.89 - 1.02 (2 H, m), 0.81 (1 H, s), 0.70 (1 H, br. s.). LC (Cond. OL3): R_t = 0.87 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{48}H_{54}ClF_4N_8O_6$: 949.38; found: 949.6. HPLC purity assessment (Cond. OL4a): R_t = 9.16 min, homogeneity index = 94.7 %. Example OL2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.86 (4 H, d, *J*=8.55 Hz), 7.79 (4 H, d, *J*=8.24 Hz), 7.29 (2 H, d, *J*=8.55 Hz), 4.95 (2 H, dd, *J*=8.55, 4.88 Hz), 4.52 (2 H, t, *J*=7.63 Hz), 3.67 (2 H, t, *J*=4.58 Hz), 3.54 (6 H, s), 2.21 - 2.40 (4 H, m), 2.01 (4 H, br. s.), 1.67 - 1.95 (13 H, m), 1.27 - 1.46 (4 H, m), 0.94 - 1.02 (2 H, m), 0.70 (2 H, d). LC (Cond. OL3): R_t = 1.01 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{48}H_{53}Cl_2F_4N_8O_6$: 983.34; found: 983.7. HPLC purity assessment (Cond. OL4a): R_t = 12.25 min, homogeneity index = 94.7 %.

Examples OL3 to OL5



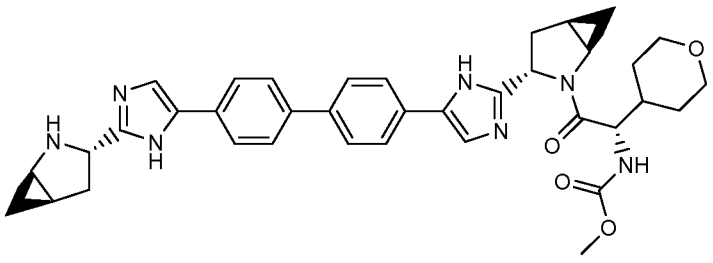
Example OL3: R_1 = R_2 = Cl
Example OL4: R_1/R_2 = Cl/H
Example OL5: R_1/R_2 = Cl/H
} Regiochemistry was not determined

Example OL3, Step a



[00435] Pyrrolidine V9a (207 mg, 0.377 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (82 mg, 0.377 mmol), HATU (158 mg, 0.415 mmol) and DIEA (0.132 mL, 0.755 mmol) were combined in DMF (5 mL) and the resulting yellow solution was stirred at ambient temperature for 3 hr. The mixture was purified by preparatory HPLC. Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: SunFire Prep MS C18 30 x 100mm 5u; Wavelength: 220nM; Flow rate: 40 mil/min; Gradient: 20% B to 80% B over 30 min. with a 2 min hold time. A white solid corresponding to the TFA salt of carbamate OL3a (0.19 g) was recovered [Note: carbamate OL3a and V9b are the same besides their form status]. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.18 (1 H, br. s.), 8.12 (1 H, s), 7.80 - 8.00 (8 H, m), 7.34 (1 H, d, *J*=8.55 Hz), 5.01 (1 H, t, *J*=8.09 Hz), 4.79 - 4.90 (1 H, m), 4.49 (1 H, t, *J*=7.48 Hz), 3.74 - 3.87 (3 H, m), 3.55 (4 H, s), 3.18 - 3.32 (2 H, m), 2.52 - 2.59 (2 H, m), 2.37 (2 H, ddd, *J*=19.99, 13.43, 6.26 Hz), 2.07 (1 H, br. s.), 1.92 (1 H, dt, *J*=13.20, 6.68 Hz), 1.73 (1 H, ddd, *J*=13.20, 6.49, 6.26 Hz), 1.06 - 1.52 (17 H, m), 0.80 (2 H, br. s.), 0.74 (1 H, br. s.). LC (Cond. OL1): R_t = 1.98 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{42}H_{50}N_7O_6$: 748.38; found: 748.52.

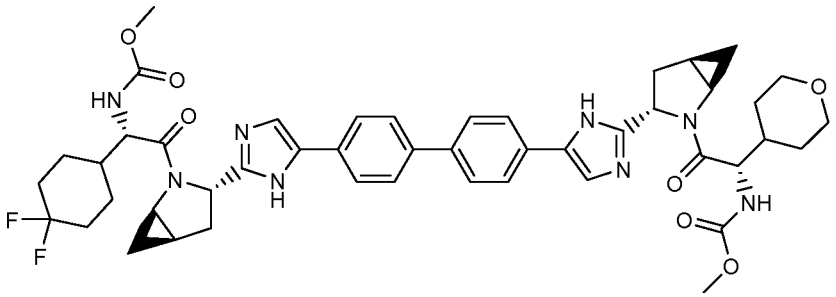
Example OL3, Step b



[00436] Carbamate OL3a (0.19 g, 0.195 mmol) was dissolved in CH_2Cl_2 (15 mL) and charged with 4N HCl in dioxanes (3 mL, 12.00 mmol). The resulting suspension was stirred at ambient temperature for 2 h and volatiles were removed under reduced pressure.

A yellowish solid corresponding to the HCl salt (3X) of pyrrolidine OL3b (0.12 g) was recovered and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.14 (1 H, s), 7.83 - 8.01 (10 H, m), 7.34 (1 H, d, *J*=8.55 Hz), 5.06 (1 H, t, *J*=7.93 Hz), 4.73 (1 H, t, *J*=8.24 Hz), 4.50 (1 H, t, *J*=7.48 Hz), 3.78 - 3.87 (3 H, m), 3.64 - 3.74 (2 H, m), 3.56 (3 H, s), 3.44 - 3.51 (1 H, m), 3.39 - 3.44 (1 H, m), 3.20 - 3.35 (2 H, m), 2.55 - 2.64 (2 H, m), 2.34 - 2.43 (1 H, m), 2.06 - 2.16 (1 H, m), 1.87 - 1.97 (2 H, m), 1.27 - 1.51 (4 H, m), 1.12 (1 H, d, *J*=4.58 Hz), 0.90 - 0.98 (1 H, m), 0.82 - 0.89 (1 H, m), 0.78 (1 H, br. s.). LC (Cond. OL2): R_t = 2.51 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{37}H_{42}N_7O_4$: 648.33; found: 648.4.

Example OL3, Step c



[00437] (S)-2-(4,4-Difluorocyclohexyl)-2-(methoxycarbonylamino)acetic acid (87 mg, 0.345 mmol), the HCl salt (3X) of pyrrolidine OL3b (261 mg, 0.345 mmol), HATU (144 mg, 0.379 mmol) and DIEA (0.301 mL, 1.724 mmol) were combined in DMF (10 mL) and the resulting brownish solution was stirred at ambient temperature for 2 h. Sample was purified directly by preparatory HPLC. Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: SunFire Prep MS C18 30 x 100mm 5u; Wavelength: 220nM; Flow rate: 40 mil/min; Gradient: 30% B to 70% B over 30 min with a 2 min hold time. A white solid corresponding to the TFA salt (2x) of amide OL3c (132 mg, 0.117 mmol, 33.8 % yield) was recovered. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.68 - 12.18 (2 H, m), 7.78 (3 H, t, *J*=8.39 Hz), 7.73 (1 H, d, *J*=9.46 Hz), 7.66 (4 H, d, *J*=8.55 Hz), 7.54 (2 H, dd, *J*=4.12, 1.68 Hz), 7.28 (2 H, dd, *J*=19.68, 8.39 Hz), 5.08 (2 H, ddd, *J*=8.39, 4.12, 3.97 Hz), 4.46 - 4.58 (2 H, m), 3.82 - 3.94 (2 H, m), 3.61 - 3.67 (2 H, m), 3.54 (6 H, d, *J*=1.53 Hz), 3.24 (2 H, t, *J*=11.29 Hz), 2.33 - 2.41 (2 H, m), 2.21 - 2.31 (2 H, m), 1.91 - 2.08 (4 H, m), 1.75 - 1.89 (6 H, m), 1.58 (1 H, d, *J*=13.43 Hz), 1.40 - 1.52 (2 H, m), 1.26 - 1.40 (3 H, m), 0.97 - 1.07 (2 H, m), 0.67 - 0.79

(2 H, m). LC (Cond. OL1): R_t = 1.94 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{47}H_{55}N_8O_7$: 881.42; found: 881.58.

Examples OL3 to OL5

[00438] NCS (22.66 mg, 0.170 mmol) was added to a solution of the TFA salt of Example OL3c (115 mg, 0.131 mmol) in DMF (3 mL) and the resulting mixture was heated to 50 °C for 5 h. The mixture was purified by preparatory HPLC. Solvent A: 05% MeCN / 95% water / 10 mM NH4Ac; Solvent B: 95% MeCN / 5% water / 10 mM NH4Ac; Column: SunFire Prep MS C18 30 X 100mm S10; Wavelength: 220nM; Flow rate: 35 ml/min; Gradient: 10% B to 100% B over 30 min with a 2 min hold time. Two fractions were isolated, where the first elute corresponded to a mixture of mono-chlorinated analogs (Examples OL4 and OL5) and the second one corresponded to the bis-chlorinated analog (Example OL3). After concentration of the corresponding fractions, the mixture was re-dissolved in methanol and the monochlorinated regioisomers were separated by preparatory HPLC. Solvent A: 10% Acetonitrile/ 90% water / 0.1% TFA; Solvent B: 90% Acetonitrile / 10% water / 0.1% TFA; Column: PHENOMENEX® Luna 21 x 100mm S10; Wavelength: 220nM; Flow rate: 25 ml/min; Gradient: 10% B to 50% B over 60 min. with a 2 min hold time. Two fractions corresponding to Example OL4 and Example OL5 were isolated as TFA and that their relative regiochemistry was not determined.

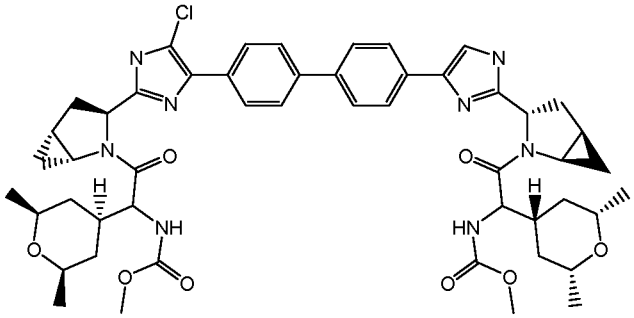
[00439] Example OL3 (36 mg) was recovered as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.55 (2 H, d, *J*=1.22 Hz), 7.87 (4 H, d, *J*=8.24 Hz), 7.78 (4 H, d, *J*=7.02 Hz), 7.27 (2 H, dd, *J*=18.62, 8.55 Hz), 5.76 (1 H, s), 4.91 - 5.01 (2 H, m), 4.45 - 4.58 (2 H, m), 3.85 (2 H, d, *J*=9.77 Hz), 3.64 - 3.71 (2 H, m), 3.54 (6 H, s), 3.20 - 3.31 (2 H, m), 2.21 - 2.35 (4 H, m), 2.02 (3 H, d, *J*=3.97 Hz), 1.59 - 1.93 (9 H, m), 1.21 - 1.55 (7 H, m), 0.93 - 1.02 (2 H, m), 0.71 (2 H, m). LC (Cond. OL3): R_t = 0.95 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{47}H_{53}Cl_2F_2N_8O_7$: 949.34; found: 949.8. HPLC purity assessment (Cond. OL4b): R_t = 11.10 min, homogeneity index = 100 %.

[00440] Example OL4 (10 mg) was recovered as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 14.62 (1 H, br. s.), 12.59 (1 H, br. s.), 8.12 (1 H, br. s.), 7.87 (8 H, dd, *J*=19.38, 8.09 Hz), 7.80 (2 H, d, *J*=7.63 Hz), 7.40 (1 H, d, *J*=8.85 Hz), 7.26 (1 H, d, *J*=8.24 Hz), 5.00 (1 H, t, *J*=7.93 Hz), 4.95 (1 H, dd, *J*=8.39, 5.04 Hz), 4.54 (1 H, t,

J=7.48 Hz), 4.49 (1 H, t, *J*=7.93 Hz), 3.86 (3 H, dd, *J*=11.44, 2.59 Hz), 3.79 (1 H, br. s.), 3.65 - 3.72 (2 H, m), 3.55 (6 H, d, *J*=5.19 Hz), 3.19 - 3.28 (2 H, m), 2.20 - 2.43 (4 H, m), 1.89 - 2.07 (5 H, m), 1.30 - 1.89 (10 H, m), 0.92 - 1.03 (2 H, m), 0.80 (1 H, br. s.), 0.72 (1 H, br. s.) LC (Cond. OL3): R_t = 0.85 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{47}H_{54}ClF_2N_8O_7$: 915.38; found: 915.9. HPLC purity assessment (Cond. OL4a): R_t = 9.03 min, homogeneity index = 100 %.

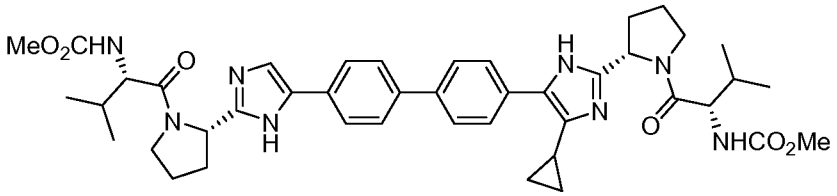
[00441] Example OL5 (12 mg, 7.96 % yield) was recovered as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 14.62 (1 H, br. s.), 12.59 (1 H, br. s.), 8.09 (1 H, br. s.), 7.87 - 7.98 (4 H, m), 7.84 (2 H, d, *J*=8.24 Hz), 7.80 (2 H, d, *J*=8.24 Hz), 7.35 (1 H, d, *J*=8.24 Hz), 7.29 (1 H, d, *J*=8.55 Hz), 4.91 - 5.03 (2 H, m), 4.51 (2 H, ddd, *J*=15.64, 7.71, 7.48 Hz), 3.78 - 3.90 (4 H, m), 3.64 - 3.71 (1 H, m), 3.54 (6 H, s), 3.16 - 3.31 (2 H, m), 2.19 - 2.44 (3 H, m), 2.02 (3 H, br. s.), 1.64 - 1.95 (7 H, m), 1.27 - 1.54 (6 H, m), 0.96 (2 H, dd, *J*=12.21, 7.32 Hz), 0.81 (1 H, br. s.), 0.70 (1 H, br. s.). LC (Cond. OL3): R_t = 0.86 min. LC-MS: Anal. Calcd. For $[M+H]^+$ $C_{47}H_{54}ClF_2N_8O_7$: 915.38; found: 915.9. HPLC purity assessment (Cond. OL4a): R_t = 8.11 min, homogeneity index = 100 %.

Example OL6

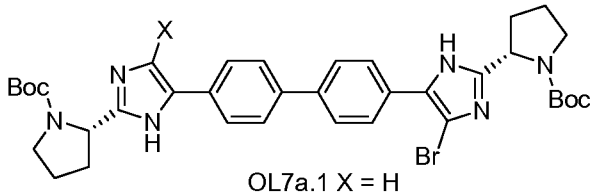


[00442] Example OL6 (TFA salt) can be prepared starting from pyrrolidine V1b/4HCl and Cap-179 (Enantiomer-1) according to the procedure described for the synthesis of Example V1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.11 (1 H, br. s.), 7.74 - 8.01 (8 H, m), 7.22 - 7.35 (1 H, m), 7.14 (1 H, d, *J*=7.53 Hz), 4.87 - 5.15 (2 H, m), 4.47 (2 H, d, *J*=7.03 Hz), 3.80 (1 H, br. s.), 3.65 (1 H, br. s.), 3.55 (6 H, br. s.), 3.36 (4 H, br. s.), 2.20 - 2.37 (3 H, m), 2.13 (1 H, br. s.), 1.90 - 2.05 (2 H, m), 1.85 (1 H, br. s.), 1.63 - 1.80 (1 H, m), 1.38 - 1.61 (2 H, m), 0.62 - 1.14 (25 H, m). LC (Cond. 2a and 2b): >95% homogeneity index. LC (Cond. OL4c): R_t = 0.85 min. LC-MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{62}ClN_8O_8$: 937.44; found: 937.5.

Example OL7



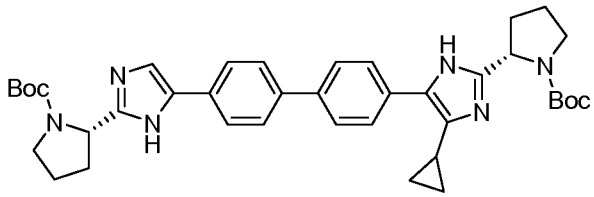
Example OL7, Step a



OL7a.1 X = H
OL7a.2 X = Br

[00443] To a solution of (2S,2′S)-*tert*-butyl 2,2′-(5,5′-(biphenyl-4,4′-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (500 mg, 0.800 mmol) in AcOH (30 mL) was added bromine (0.041 mL, 0.800 mmol) in AcOH (0.8 mL) dropwise over 10 min. The resulting reaction mixture was stirred at room temperature overnight, neutralized with sat. $NaHCO_3$, then extracted with CH_2Cl_2. The organic layers was dried with $MgSO_4$ and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (silica gel; 1:1 EtOAc/Hex then 2:1 EtOAc/Hex) to afford bromide OL7a.1 (200 mg) and dibromide OL7a.2 (140 mg) as white solids (note: the dibromide eluted first from column).

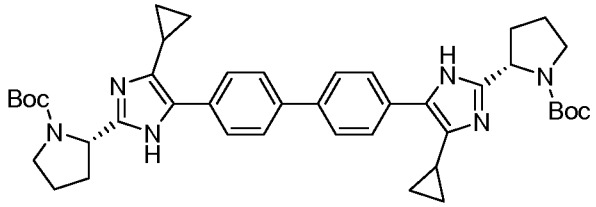
Example OL7, Step b.1



[00444] A mixture of cyclopropylboronic acid (13.49 mg, 0.157 mmol), potassium phosphate tribasic (90 mg, 0.423 mmol) in water (0.03 mL) was stirred at room temperature for 15 min. Bromide OL7a.1 (85 mg, 0.121 mmol), Pd(II)acetate (2.71 mg, 0.012 mmol), tricyclohexylphosphine (6.8 mg, 0.024 mmol) and toluene (1 mL) were

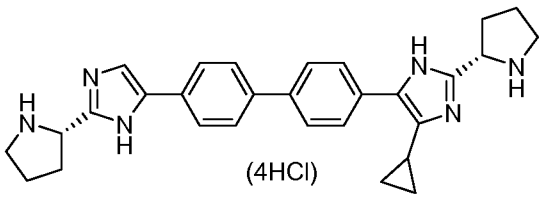
then added, and the reaction mixture was stirred at 110 °C overnight. The volatile component was removed *in vacuo* and the residue was purified by preparative HPLC using the following condition. Column: Waters SunFire OBD 19 X 100 mm S5; Solvent A = 10%ACN-90%H_2O-0.1%TFA; Solvent B = 90%ACN-10%H_2O-0.1%TFA; Start %B = 10; Final %B = 75; Flow rate = 20 ml/min; Gradient time = 20 min. The TFA salt of the coupled product OL7b.1 was retrieved as a light yellow solid (79 mg).

Example OL7, Step b.2



[00445] A mixture of dibromide OL7a.2 (140 mg, 0.179 mmol), cyclopropylboronic acid (40.0 mg, 0.465 mmol), Pd(II)acetate (8.03 mg, 0.036 mmol), potassium phosphate tribasic (266 mg, 1.252 mmol), tricyclohexylphosphine (20.07 mg, 0.072 mmol) in toluene (1.5 mL) and Water (0.05 mL) was heated with a microwave at 110 °C for 1.5 hours. LCMS showed that there is no reaction. The mixture was filtered, and the filtrate was concentrated *in vacuo* and the resultant crude product was purified by prep. HPLC: Column = Waters SunFire OBD 19 X 100 mm S5; Solvent A = 10%ACN-90%H_2O-0.1%TFA; Solvent B = 90%ACN-10%H_2O-0.1%TFA; Start %B = 10. Final %B = 70; Flow rate = 20 ml/min; Gradient time = 20 min. The TFA salt of the coupled product OL7b.2 was obtained as a light yellow solid.

Example OL7, Step c



[00446] To a solution of carbamate OL7b prepared above (79 mg) in CH_2Cl_2 (2 mL) was added HCl (2 mL, 8.00 mmol) (4 N in dioxane), and the resulting mixture was stirred at room temperature for 30 mins. The volatile component was removed *in vacuo* to afford

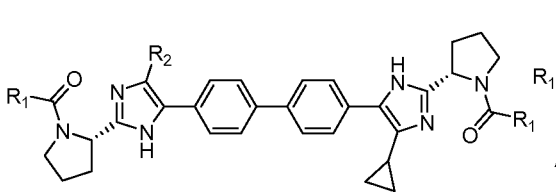
the HCl salt of OL7c (69 mg), which was used in the next step without further purification.

Example OL7

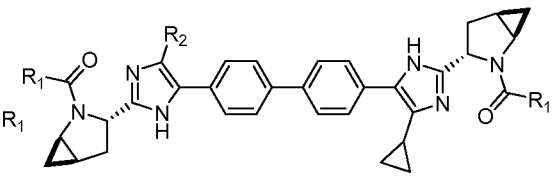
[00447] To a mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (20.09 mg, 0.115 mmol), pyrrolidine OL7/4 HCl (35 mg, 0.057 mmol) in DMF (1 mL) was added DiPEA (0.06 mL, 0.34 mmol) and HATU (43.6 mg, 0.115 mmol). The reaction mixture was stirred at room temperature for 1 hour, and then ammonia (2 mL, 2 M in Methanol) was added, and stirring was continued for an additional 1 hour. The volatile component was removed *in vacuo*, and the residue was purified by preparative HPLC: Column = Waters SunFire C18 19 X 100 mm 5u; Solvent A = 10%MeOH-90%H_2O-0.1%TFA; Solvent B = 90%MeOH-10%H_2O-0.1%TFA; Start %B = 10; Final %B = 75; Flow rate = 25 ml/min; Gradient time = 18 min. The TFA salt of Example OL7 was obtained as an off-white solid (24 mg). Rt = 1.68 min (Cond. OL5a). $(M+H)^+$ 779.47. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.12 (1 H, br. s.), 7.97 (4 H, dd, *J*=12.97, 8.39 Hz), 7.86 - 7.92 (2 H, m), 7.80 (2 H, d, *J*=8.24 Hz), 7.32 (2 H, t, *J*=8.70 Hz), 5.14 (1 H, t, *J*=7.02 Hz), 5.05 (1 H, t, *J*=7.48 Hz), 4.12 (2 H, t, *J*=6.71 Hz), 3.76 - 3.92 (4 H, m), 3.54 (6 H, s), 2.39 (2 H, d, *J*=6.10 Hz), 1.95 - 2.21 (9 H, m), 1.08 (2 H, d, *J*=8.24 Hz), 0.84 (7 H, t, *J*=7.17 Hz), 0.79 (6 H, d, *J*=6.41 Hz), 0.67 - 0.74 (1 H, m)

Examples OL8 to OL14

[00448] Examples OL8 to OL14 were prepared as TFA salts by employing appropriate precursors and the procedure described for the preparation of Example OL7.

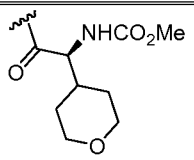
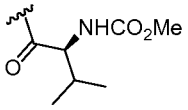
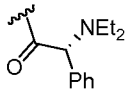
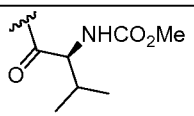
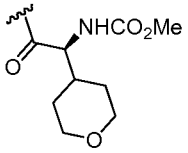
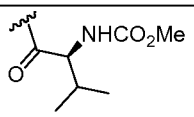
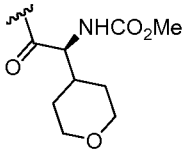


Example OL8-OL10

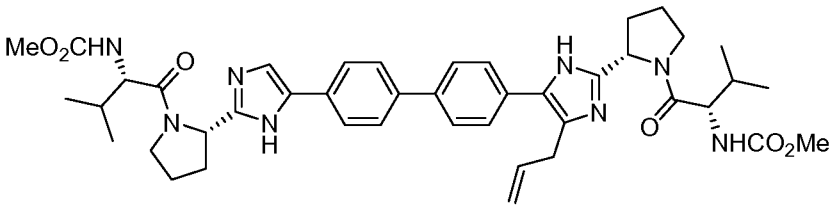


Example OL11-OL14

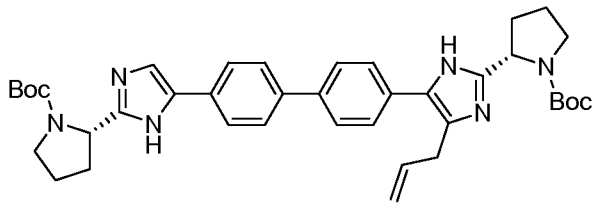
Example		R_2	Rt(Condition). LC-MS $(M+H)^+$ observed

Example		R_2	Rt(Condition). LC-MS $(M+H)^+$ observed
OL8		H	Rt = 1.49 min (Cond. OL5a). $(M+H)^+$ 863.48
OL9			Rt = 1.77 min (Cond. OL5a). $(M+H)^+$ 819.55
OL10			Rt = 1.54 min (Cond. OL5a). $(M+H)^+$ 883.51
OL11		H	Rt = 1.74 min (Cond. OL5a). $(M+H)^+$ 803.41
OL12		H	Rt = 2.40 min (Cond. OL5b). $(M+H)^+$ 887.60
OL13			Rt = 1.87 min (Cond. OL5a). $(M+H)^+$ 843.39
OL14			Rt = 2.55 min (Cond. OL5b). $[(M+H)/2]^+$ = 464.36

Example OL15



Example OL15, Step a

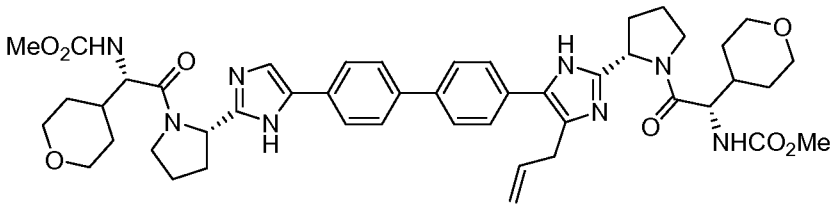


[00449] A mixture of bromide OL7a.1 (200 mg, 0.284 mmol), CsF (0.021 mL, 0.568 mmol), $Pd(Ph_3P)_4$ (19.71 mg, 0.017 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.107 mL, 0.568 mmol) in THF (3 mL) was heated at 140 °C in microwave for 1 hour. The solvent was removed *in vacuo*, and the residue was purified by preparative HPLC. Column, PHENOMENEX® Luna 10u (30 X 100 mm); Solvent A = 5%CH_3CN-95%H_2O-10mmNH_4Oac; Solvent B = 95%CH_3CN-5%H_2O-10mmNH_4OAc; Start %B = 30; Final %B = 100; Flow rate = 25 ml/min; Gradient time = 48 min. Product OL15a was obtained as a white solid (90 mg).

Example OL15

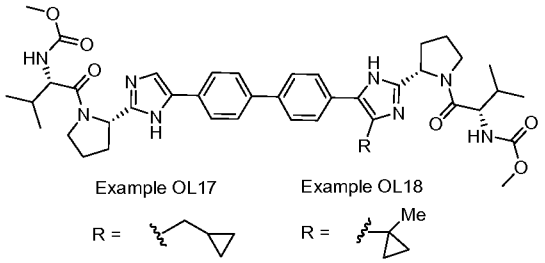
[00450] Carbamate OL15a was elaborated to the TFA salt of Example OL15 according to the procedure described for the synthesis of Example OL7. Rt = 1.73 min (Cond. OL5a). $(M+H)^+$ 779.53.

Example OL16



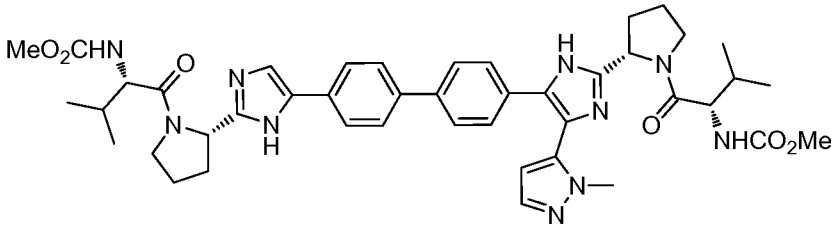
[00451] Example OL16 (TFA salt) was prepared from appropriate precursors according to the procedure described for the synthesis of Example OL15. Rt = 1.73 min (Cond. OL5a). $(M+H)^+$ 863.11.

Examples OL17 and OL18

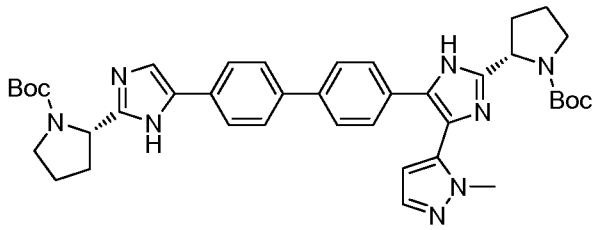


[00452] To a solution of OL15a (70 mg, 0.105 mmol), diiodomethane (0.102 mL, 1.263 mmol) in toluene (0.5 mL) at 0 °C was quickly added diethylzinc (1.263 mL, 1.263 mmol) (1 M in heptane). The resulting mixture was stirred at 0 °C for 1.5 hour then at room temperature for 4 hours. To the mixture was added a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried under $MgSO_4$ and concentrated. The residue was purified by preparatory HPLC: Column, PHENOMENEX® Luna 10u (30 X 100 mm); Solvent A = 5%CH_3CN-95%H_2O-10mm NH_4Oac; Solvent B = 95%CH_3CN-5%H_2O-10mmNH_4OAc; Start %B = 30; Final %B = 100; Flow rate = 25 ml/min. Gradient time = 25 min. The resultant material (white solid, 40 mg) was dissolved in CH_2Cl_2 (1 mL) and treated with HCl (1 mL, 4.00 mmol) (4 N in dioxane). The mixture was stirred at room temperature for 1 hour. The volatile component was removed *in vacuo* to afford a product (35 mg), which was coupled with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid according to the procedure described for the synthesis of Example OL7. The obtained crude residue was purified by preparative HPLC: Column = Waters SunFire C18 19 X 100 mm 5u; Solvent A = 10%MeOH-90%H_2O-0.1%TFA; Solvent B = 90%MeOH-10%H_2O-0.1%TFA; Start %B = 20; Final %B = 85; Flow rate = 25 ml/min; Gradient time = 27 min. Two fractions were isolated, where the first one to elute corresponded to the TFA salt of Example OL18 (Rt = 1.74 min (Cond. OL5a). $(M+H)^+$ 793.54) and the second one to elute corresponded to the TFA salt of Example OL17 (Rt = 1.77 min (Cond. OL5a). $(M+H)^+$ 793.53).

Example OL19

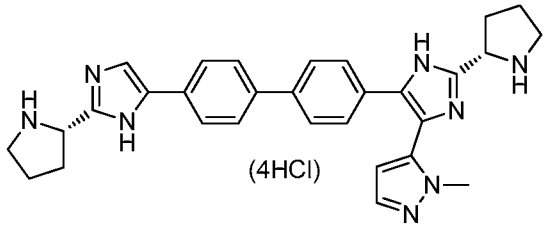


Example OL19, Step a



[00453] A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (59.1 mg, 0.284 mmol), potassium phosphate tribasic (121 mg, 0.568 mmol) in water (0.2 mL) was stirred at room temperature for 15 min. Bromide OL7a.1 (100 mg, 0.142 mmol), $Pd(Ph_3P)_4$ (9.85 mg, 0.008 mmol and DMF (2 mL) were then added, and the reaction mixture was stirred for 40 min. at 130 °C under microwave radiation. The volatile component was removed *in vacuo* and the residue was purified by preparative HPLC using the following condition. Column: PHENOMENEX® Luna 10u (30 X 100 mm); Solvent A = 10%ACN-90%H_2O-10 mm NH_4OAc; Solvent B = 90%ACN-10%H_2O-10mmNH_4OAc; Start %B = 10; Final %B = 80; Flow rate = 25 ml/min; Gradient time = 15 min. The coupled product OL19a was retrieved as a light yellow solid (120 mg).

Example OL19, Step b



[00454] To a solution of carbamate OL19a prepared above (120 mg) in CH_2Cl_2 (1 mL) was added HCl (1 mL, 4.00 mmol) (4 N in dioxane), and the resulting mixture was stirred at room temperature for 1h. The volatile component was removed *in vacuo* to afford the HCl salt of OL19b (87 mg), which was used in the next step without further purification.

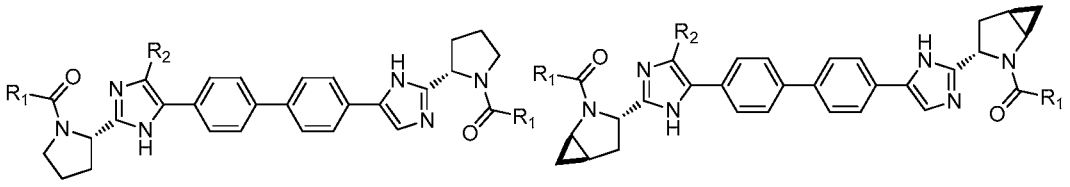
Example OL19

[00455] To a mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (15.30 mg, 0.087 mmol), pyrrolidine OL19b/4 HCl (30 mg, 0.044 mmol) in DMF (1 mL) was

added DiPEA (0.053 mL, 0.306 mmol) and HATU (33.2 mg, 0.087 mmol). The reaction mixture was stirred at room temperature for 1 hour, the volatile component was removed *in vacuo*, and the residue was purified by preparative HPLC: Column = Waters Atlantis OBD 30 X 100 mm 5u; Solvent A = 10%MeOH-90%H_2O-0.1%TFA; Solvent B = 90%MeOH-10%H_2O-0.1%TFA; Start %B = 20; Final %B = 75; Flow rate = 25 ml/min; Gradient time = 25 min. The TFA salt of Example OL19 was obtained as a white solid (33 mg). Rt = 1.63 min (Cond. OL5a). $(M+H)^+$ 819.40. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.13 (1 H, s), 7.88 - 7.96 (2 H, m), 7.78 - 7.88 (4 H, m), 7.57 (1 H, br. s.), 7.43 - 7.51 (2 H, m), 7.33 (2 H, dd, *J*=8.39, 3.51 Hz), 6.42 (1 H, br. s.), 5.10 - 5.18 (2 H, m), 4.11 (2 H, td, *J*=7.93, 2.75 Hz), 3.78 - 3.91 (4 H, m), 3.59 - 3.66 (3 H, m), 3.54 (6 H, d, *J*=1.53 Hz), 2.35 - 2.45 (1 H, m), 2.30 (1 H, d, *J*=7.32 Hz), 2.13 - 2.22 (2 H, m), 1.93 - 2.13 (6 H, m), 0.89 (5 H, d, *J*=6.71 Hz), 0.83 (6 H, t, *J*=6.87 Hz), 0.78 (3 H, d, *J*=6.71 Hz).

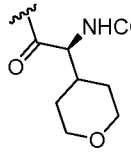
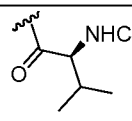
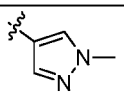
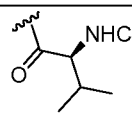
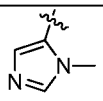
Examples OL20 to OL25

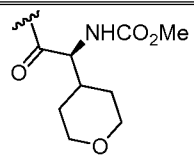
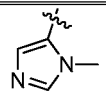
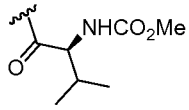
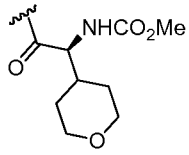
[00456] Examples OL20 to OL25 were prepared as TFA salts by employing appropriate precursors and the procedure described for the preparation of Example OL19.



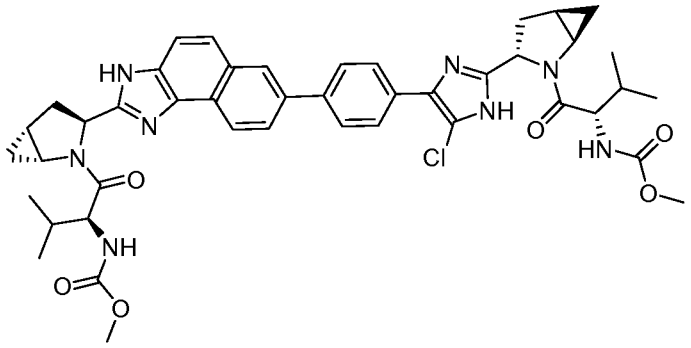
Example OL20-OL23

Example OL24-OL25

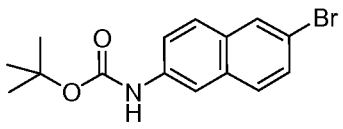
Example		R_2	Rt(Condition). LC-MS $(M+H)^+$ observed
OL20			Rt = 2.19 min (Cond. OL5b). $(M+H)^+$ 903.65
OL21			Rt = 1.56 min (Cond. OL5a). $(M+H)^+$ 819.39
OL22			Rt = 1.43 min (Cond. OL5a). $(M+H)^+$ 816.66

Example		R_2	Rt(Condition). LC-MS $(M+H)^+$ observed
OL23			Rt = 1.27 min (Cond. OL5a). $(M+H)^+$ 903.61
OL24			Rt = 1.83 min (Cond. OL5a). $(M+H)^+$ 830.50
OL25			Rt = 1.62 min (Cond. OL5a). $[(M+H)/2]^+$ 457.6

Example DSTL-1



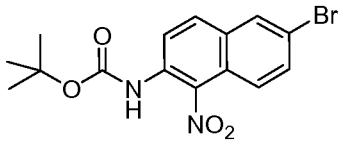
Example DSTL-1, Step a



[00457] Diphenylphosphoryl azide (17.09 mL, 79 mmol) was added to a solution of 6-bromo-2-naphthoic acid (16.5 g, 65.7 mmol), triethylamine (18.32 mL, 131 mmol), and *tert*-butylalcohol (7.54 mL, 79 mmol) in toluene (225 mL) and stirred for 4 h at 100 °C. The volatiles were removed by rotary evaporation and the residue taken up in EtOAc (500 mL) and washed with water and brine. A precipitate formed upon concentration which was isolated by filtration and washed with 1:1 Et_2O/Hex to give Example DSTL-1, Step a (10.5 g). A second crop of less pure product was isolated upon concentration of

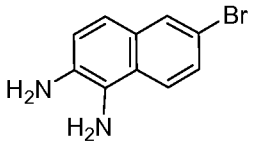
the mother liquor (9.8 g); combined yield (93%). LC-MS (Cond.-J4): RT = 3.44 min. LC-MS Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{16}BrNO_2$: 345.02; found 345.03.

Example DSTL-1, Step b



[00458] Example DSTL-1, Step a (5 g, 15.52 mmol) was diluted in acetic acid (50 mL) and fuming nitric acid (2.3 mL) was added dropwise over 20 min. The reaction was stirred for 2 h and the product, isolated by filtration, was partitioned between DCM and sat'd $NaHCO_3$ soln. The organic layer was concentrated and Example DSTL-1, Step b was obtained 5.7 g (quant). LC-MS (Cond.-J4): RT = 3.52 min. LC-MS Anal. Calcd. for $[M+Na]^+$ $C_{15}H_{15}BrN_2O_4$: 390.02.; found 390.99.

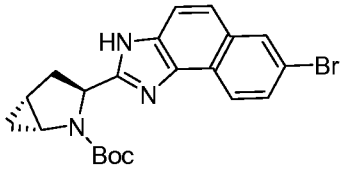
Example DSTL-1, Step c



HCl salt

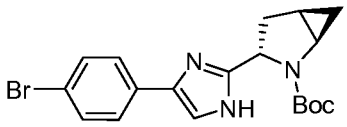
[00459] Tin(II)chloride dehydrate (3 g, 16.34 mmol) was added to a solution of Example DSTL-1, Step b (2 g, 5.47 mmol) in MeOH (100 mL) and the solution was stirred for 18 h at 70 °C. The solvent was removed by rotary evaporation and Example DSTL-1, Step c (assume theoretical 1.25 g) was dried under high vacuum. LC-MS (Cond.-J4): RT = 1.49 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{10}H_9BrN_2$: 237.00; found 236.96.

Example DSTL-1, Step d



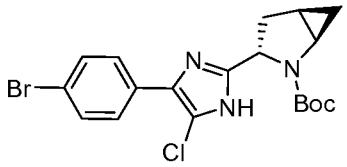
[00460] HATU (2.085 g, 5.48 mmol) was added to a solution of Example DSTL-1, Step c (1.25 g, 5.48 mmol), Example 1, Step b (1.246 g, 5.48 mmol), and Hunig's base (7.09 g, 54.8 mmol) in DMF (70 mL) and the reaction mixture was stirred for 6 h before being partitioned between EtOAc (500 mL) and sat'd $NaHCO_3$ (150 mL). The tin salts that precipitated were removed by filtration through CELITE®, and the organic phase was concentrated to yield a residue which was taken up in AcOH (100 mL) and heated at 60 °C for 18 h. The solvent was removed by rotary evaporation under high vacuum, and residue taken up in CH_2Cl_2 and washed with sat'd $NaHCO_3$ soln. After concentration, the crude product was charged (DCM) to a Thompson silica gel cartridge (110 g) and subject to gradient elution; 15 - 100% B over 1 L to give Example DSTL-1, Step d (420 mg, 44 %). LC-MS (Cond.-J4): RT = 2.51 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_3O_2$: 430.10.; found 430.06.

Example DSTL-1, Step d.1



[00461] Example DSTL-1, Step d.1 was prepared from Example 1, Step b according to the procedure described for the synthesis of its desmethano analog in patent application WO 2008/021927.

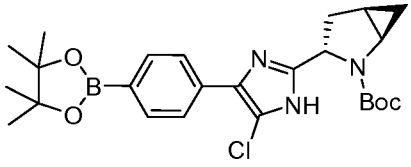
Example DSTL-1, Step e



[00462] To a solution of Example DSTL-1, Step d.1 (560 mg, 1.39 mmol) in DMF (15 mL) was added NCS (203 mg, 1.52 mmol). The reaction mixture was heated at 50 °C for 16 h. The solution was purged with nitrogen to evaporate DMF, and the crude residue was charged (DCM) to a Thompson SiO_2 column (80 g) and gradient elution performed (BIOTAGE®). Segment 1: 10 - 100% B over 1.5 L. Segment 2: Hold 100% B 300 mL. (A/B Hexanes/EtOAc). There was isolated Example DSTL-1, Step e (589.1 mg, 92 %

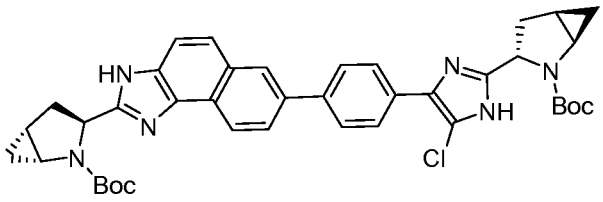
yield). LC-MS (Cond.-D4): RT = 2.61 min. LC-MS Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{22}ClN_3O_2$: 462.04; found 462.07.

Example DSTL-1, Step f



[00463] Tetrakis(triphenylphosphine) palladium (76 mg, 0.066 mmol) was added in one portion to a stirred suspension of Example DSTL-1, Step e (580 mg, 1.32 mmol), bis(pinacolato)diboron (671 mg, 2.64 mmol) and potassium acetate (324 mg, 3.30 mmol) in a solution of dioxane (12 mL) in a screw-capped pressure vessel. The reaction mixture was evacuated and flushed with argon (3x) and placed into a pre-heated oil bath (80 °C) and stirred for 16 h. Upon cooling, the reaction mixture was diluted with EtOAc, washed with sat'd $NaHCO_3$ soln, brine and dried over Na_2SO_4. The crude residue was charged (DCM) to a Thompson SiO_2 column (80 g) and gradient elution performed (BIOTAGE®). Segment 1: 5 - 100% B over 1.5 L. Segment 2: Hold 100% B 300 mL. (A/B CH_2Cl_2/EtOAc). There was isolated Example DTSL-1, Step f (714.7 mg, 95%) as yellow foam. LC-MS (Cond.-D4): RT = 2.69 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{25}H_{34}BClN_3O_4$: 486.24; found 486.26.

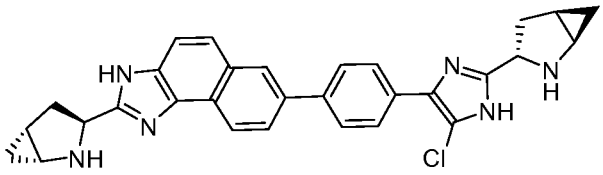
Example DSTL-1, Step g



[00464] Tetrakis(triphenylphosphine) palladium (27.0 mg, 0.023 mmol) was added in one portion to a stirred suspension of Example DSTL-1, Step d (200 mg, 0.467 mmol), Example DSTL-1, Step f (250 mg, 0.514 mmol) and $NaHCO_3$ (196 mg, 2.335 mmol) in a degassed solution of DME (4 mL) and water (1 mL) under argon in a screw-capped pressure vessel. The solution was evacuated and charged with argon (3x) and placed into a pre-heated oil bath (80 °C) and stirred for 14 h. The mixture was diluted with EtOAc

(10 mL), THF (2 mL) and MeOH (1 mL), washed with brine and dried over Na_2SO_4. After concentration to remove solvent, the residue was charged to a Thompson SiO_2 column (80 g) and eluted (BIOTAGE®) by gradient. Segment 1: 20 - 100% B over 1.5 L, Segment 2: hold 100% B for 300 mL; A/B Hexanes/EtOAc. There was isolated DSTL-1, Step g (195.0 mg, 52.6%) as a tan solid. LC-MS (Cond.-D4): RT = 2.40 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}ClN_6O_4$: 707.31; found 707.43.

Example DSTL-1, Step h



HCl salt

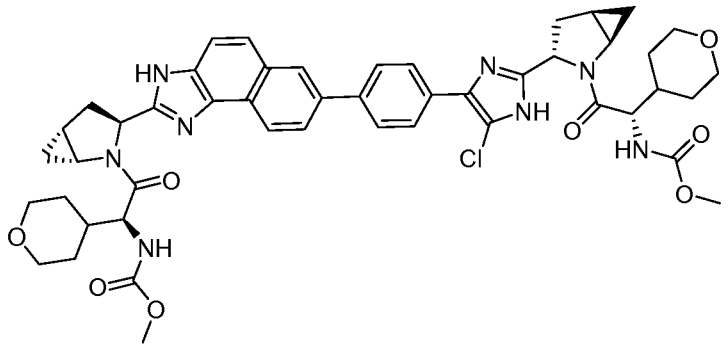
[00465] Cold (0 °C) 4*N* HCl in dioxane (4 mL) was added to a stirred solution of Example DSTL-1, Step g (65 mg, 0.092 mmol) in MeOH (1 mL). The mixture was stirred at rt for 3 h, concentrated, and placed under high vacuum to provide DSTL-1, Step h as an orange-tan solid and as a tetra HCl salt. LC-MS (Cond.-D4): RT = 1.63 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{30}H_{28}ClN_6$: 507.21; found 507.26.

Example DSTL-1

[00466] Example DSTL-1 was prepared from Example DSTL-1, Step h according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. %). There was isolated Example DSTL-1 (70.4 mg, 67.7%) as a white solid. ^1H NMR (MeOD, 500 MHz, δ): 8.47 (d, *J* = 8.6 Hz, 1H), 8.44 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 1H), 5.34-5.31 (m, 1H), 5.07 (t, *J* = 7.32 Hz, 1H), 4.61 - 4.58 (m, 2H), 3.39-3.31 (m, 1H), 3.75-3.72 (m, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.83-2.81 (m, 1H), 2.64-2.59 (m, 1H), 2.49-2.48 (m, 2H), 2.23-2.14 (m, 3H), 2.05-2.03 (m, 1H), 1.18-1.12 (m, 2H), 1.05-0.92 (m, 13H), 0.83-0.81 (m, 1H). LC-MS

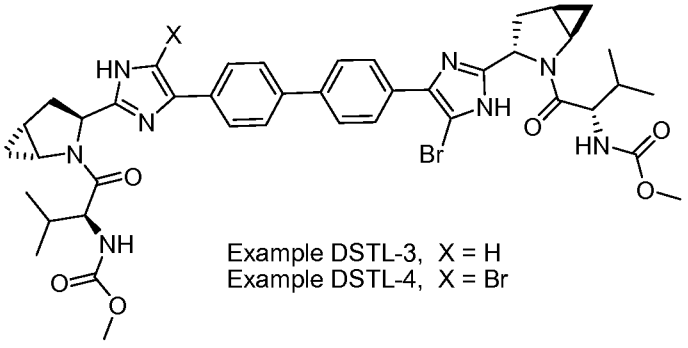
(Cond.-D4): RT = 2.24 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{50}ClN_8O_6$: 821.36; found 821.54.

Example DSTL-2

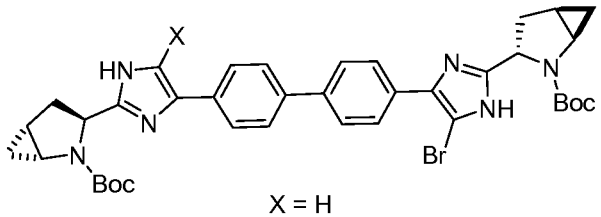


[00467] Example DSTL-2 was prepared from Example DSTL-1, Step h according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated Example DSTL-2 (18.0 mg) as a white solid. LC-MS (Cond.-D4): RT = 2.04 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{48}H_{54}ClN_8O_6$: 905.38; found 905.60.

Examples DSTL-3 and DSTL-4



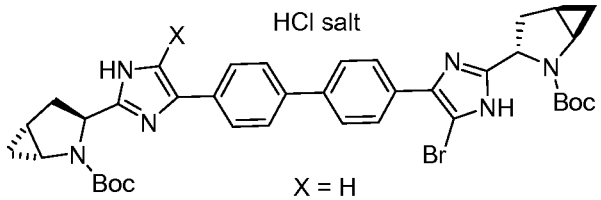
Examples DSTL-3, Step a and DSTL-4, Step a



X = H
X = Br

[00468] A solution of bromine (0.079 mL, 1.54 mmol) in AcOH (1 mL) was added portionwise to a stirred solution of Example 1, Step d (1.0 g, 1.541 mmol) in AcOH (40 mL), and the mixture was stirred at rt for 3 h. The solvent was removed *in vacuo* and the residue was taken up in DCM and washed with sat'd $NaHCO_3$ soln. The aqueous layer was extracted twice more with DCM and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue was charged (DCM) to a Thompson silica gel cartridge (160 g) and eluted with 30 - 100% B over 2 L. Segment 2: hold 100% B for 800 mL. A/B Hexanes/EtOAc. There was isolated 3 components; Starting material (303.6 mg); Example DSTL-3, Step a (X = H; 382.1 mg); yellow solid. LC-MS (Cond.-D4): RT = 2.21 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{44}BrN_6O_4$: 729.26; found . 729.28; Example DTSL-4, Step a (X = Br; 287.2 mg); light, yellow solid. LC-MS (Cond.-D4): RT = 2.62 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}Br_2N_6O_4$: 807.17; found: 807.33.

Examples DSTL-3, Step b and DSTL-4, Step b



X = H
X = Br

[00469] The products of Example DSTL-3, Step b and DSTL-4, Step b were brought forward separately. Removal of the protecting groups was performed as described in the procedure from Example DSTL-1, Step h. X = H; Example DTSL-3, Step b: Yellow solid, 33.1 mg (97% pure); LC-MS (Cond.-D4): RT = 1.49 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{28}BrN_6$: 529.16; found 529.24. X = Br; Example DTSL-4, Step b: Yellow solid, 33 mg (96% pure); LC-MS (Cond.-D4): RT = 1.82 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{27}Br_2N_6$: 607.07; found 607.16.

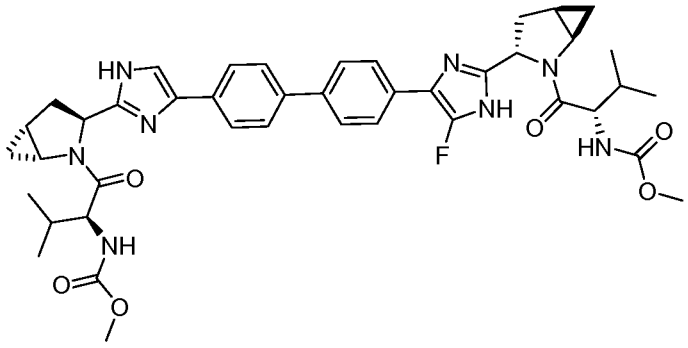
Example DSTL-3

[00470] Example DSTL-3 was prepared from Example DSTL-3, Step b according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC; 0% - 50%B over a 30 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%TFA. There was isolated Example DSTL-3 (29.0 mg) as a white solid. LC-MS (Cond.-D4): RT = 2.07 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}BrN_8O_6$: 843.30; found 843.39.

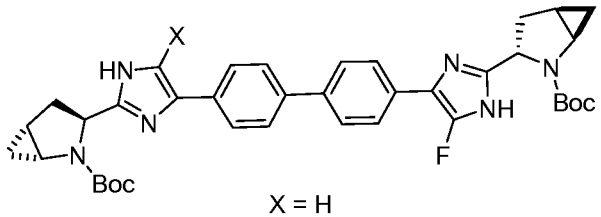
Example DSTL-4

[00471] Example DSTL-4 was prepared from Example DSTL-4, Step b according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC; 0% - 50%B over a 30 min gradient at 40ml/min using a Waters SunFire column (30 x 100 mm, S5) B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%TFA. There was isolated Example DSTL-4 (30.2 mg) as a white solid. ^1H NMR (MeOD, 500 MHz, δ): 7.82 (s, 8H), 5.08-5.05 (m, 2H), 4.58 (app d, *J* = 6.7 Hz, 2H), 3.76-3.74 (m. 2H), 3.67 (s, 6H), 2.57-2.52 (m, 2H), 2.50-2.44 (m, 2 H), 2.22-2.17 (m, 2H), 2.06-2.01 (m, 2H), 1.12-1.08 (m, 2H), 1.04 (d, *J* = 6.7 Hz, 6H), 0.95 (d,, *J* = 6.7 Hz, 6H), 0.84-0.82 (m, 2H). LC-MS (Cond.-D4): RT = 2.56 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}BrN_8O_6$: 921.31; found 921.30.

Example DSTL-5



Example DSTL-5, Step a



X = H
X = F

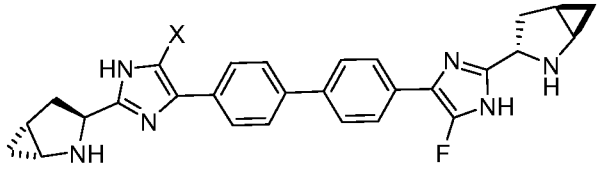
[00472] Accufluor (45-50% on alumina) (345 mg, 1.2 mmol) was added in one portion to a stirred suspension of Example 1, Step d, (1R,1′R,3S,3′S,5R,5′R)-*tert*-butyl 3,3′-(5,5′-(biphenyl-4,4′-diyl)bis(1H-imidazole-5,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (500 mg, 0.77 mmol) in dry DMF (5 mL) at rt. The mixture was placed into a preheated oil bath at 60 °C and stirred 4 h before the solvent was removed by rotary evaporation under high vacuum The crude product was charged to a Thompson 90 g silica gel cartridge and eluted 10 – 100 % B over 2 L, and hold 100% B for 1 L (Solvent B = EtOAc; Solvent A = hexanes). A second gradient was applied eluting 0 – 100 % B over 2 L (Solvent B = methanol; Solvent A = EtOAc). Three fractions were collected: Example DSTL-5, Step a (X=F), (1R,1′R,3S,3′S,5R,5′R)-*tert*-butyl 3,3′-(5,5′-(biphenyl-4,4′-diyl)bis(4-fluoro-1H-imidazole-5,2-diyl))bis(2-azabicyclo[3.1.0]hexane-2-carboxylate) (45.0 mg, 7 %) as a yellow solid; Example DSTL-5, Step a (X=H) ((1R,3S,5R)-*tert*-butyl 3-(5-(4′-(2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-4-fluoro-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (193 mg, 32 %) as a yellow solid, and recovered starting material (153 mg, 24 %).

[00473] Example DSTL-5, Step a X = F: A sample (~10 mg) of the first eluting compound was further purified by preparative HPLC (0 - 100% B) over a 30 min gradient (at 40ml/min) using a PHENOMENEX® Luna column (30 x 100 mm, 10u) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated (4.6 mg) as a light yellow solid. LC-MS (Cond.-D4): RT = 4.43 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}F_2N_6O_4$: 685.33; found 685.38.

[00474] Example DSTL-5, Step a X = H: A sample (~15 mg) of the second eluting compound was further purified by preparative HPLC (0 - 100% B) over a 30 min gradient (at 40ml/min) using a PHENOMENEX® Luna column (30 x 100 mm, 10u) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%

TFA. There was isolated (11.2 mg) as an off-white solid. LC-MS (Cond.-D4): RT = 4.43 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{44}FN_6O_4$: 667.34; found 667.40.

Example DSTL-5, Step b



X = H
X = F

[00475] The products of Example DSTL-5, Step a, (X = F) and (X = H), were brought forward separately. Removal of the protecting groups was performed as described in the procedure from Example DSTL-1, Step h.

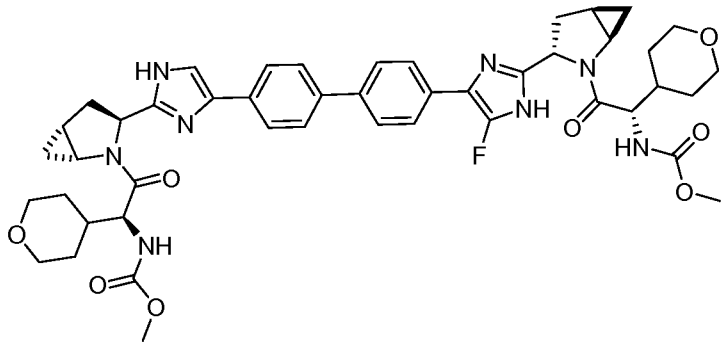
[00476] Example DTSL-5, Step b (X = F): Yellow solid, 23.4 mg; LC-MS (Cond.-D4): RT = 2.89 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{27}F_2N_6$: 485.22; found 485.25.

[00477] Example DTSL-5, Step b (X = H): 18 mg (95% pure); LC-MS (Cond.-D4): RT = 2.55 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{28}FN_6$: 467.25; found 467.27.

Example DSTL-5

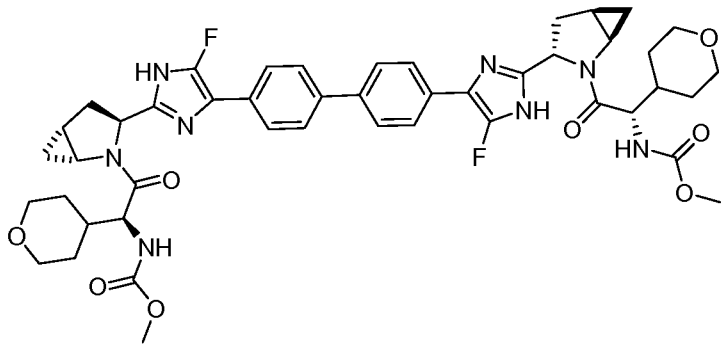
[00478] Example DSTL-5 was prepared from Example DSTL-5, Step b (X = H) according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC; 0% - 50%B over a 30 min gradient at 40ml/min using a Waters SunFire column (30 x 100 mm, S5) B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%TFA. There was isolated Example DSTL-5 (37.3 mg, 39%) as a pale yellow solid. ^1H NMR (MeOD, 500 MHz, δ): 7.88 (s, 1 H), 7.84 (d, *J*=8.5 Hz, 2H), 7.80 (d, *J*=8.5 Hz, 2H), 7.77 (d, *J*=8.5 Hz, 2H), 7.68 (d, *J*=8.5, 2H), 5.13 (t, *J*=7.0 Hz, 1H), 5.04 (t, *J*= 6.1Hz, 1H), 4.56 (d, *J*= 6.7 Hz, 2H) 3.82 (br. s, 1H), 3.68-3.67 (m, 7H), 2.72-2.68 (m, 1H), 2.51-2.43 (m, 3H), 2.21-2.14 (m, 2H), 2.09 (br. s, 1H), 2.03 (br. s, 1H), 1.15-1.09 (m, 2H), 1.02 (d, *J*=6.7 Hz, 6H), 0.94 (t, J=7.0 Hz, 6H), 0.90 (br. s, 1H), 0.81 (br. s, 1H). LC-MS (Cond.-D4): RT = 3.45 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}FN_8O_6$: 781.39; found 781.54.

Example DSTL-6



[00479] Example DSTL-6 was prepared from Example DSTL-5, Step b (X = H) according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated Example DSTL-6 (37.1 mg, 36%) as a white solid. LC-MS (Cond.-D4): RT = 3.17 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{48}H_{54}FN_8O_6$: 865.41; found 865.55.

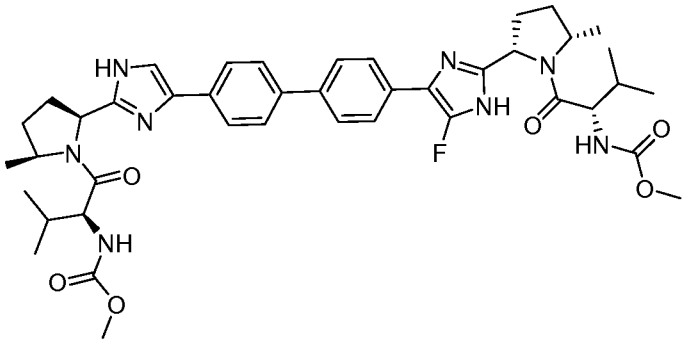
Example DSTL-7



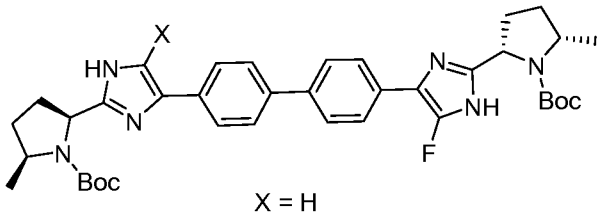
[00480] Example DSTL-7 was prepared from Example DSTL-5, Step b (X = F) according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated Example DSTL-7 (14 mg, 25%) as a white solid. ^1H NMR (MeOD,

500 MHz, δ) 7.72 (d, *J*=8.5 Hz, 4H), 7.64 (d, *J*=8.5 Hz, 4H), 5.03 (t, *J*=6.7 Hz, 2H), 4.63 (d, *J*= 7.6 Hz, 2H), 3.97-3.93 (m, 4H), 3.72 (br. s, 2H). 3.67 (s, 6H), 3.42-3.37 (m, 4H), 2.44-2.42 (m, 4H), 2.02 (br. s, 4H),1.63-1.57 (m, 6H), 1.46-1.43 (m, 2H), 1.14-1.19 (m, 2H), 0.80 (br. s, 2H): LC-MS (Cond.-D4): RT = 3.17 min. LC-MS Anal. Calcd. for [M+H]$^+$ $C_{46}H_{53}F_2N_8O_6$: 883.40; found 883.57.

Example DSTL-8



Example DSTL-8, Step a

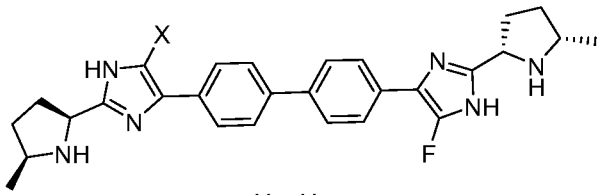


X = H
X = F

[00481] Accufluor (45-50% on alumina) (274 mg, 0.92 mmol) was added in one portion to a stirred suspension of Example GW1, Step a, (2S,2′S,5S,5′S)-*tert*-butyl 5,5′-(5,5′-(biphenyl-4,4′-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpyrrolidine-1-carboxylate) (400 mg, 0.6 mmol) in dry DMF (4 mL) at rt. The mixture was placed into a preheated oil bath at 60 °C and stirred 4 h before an additional 135 mg of Accufluor was added and stirring was continued at 60 °C for 16 h. The solvent was removed by rotary evaporation under high vacuum, and the crude product was charged to a Thompson 90 g silica gel cartridge and eluted 10 – 100 % B over 2 L, and hold 100% B for 1 L (Solvent B = EtOAc; Solvent A = hexanes). A second gradient was applied eluting 0 – 100 % B over 2 L (Solvent B = methanol; Solvent A = EtOAc). Three fractions were collected: Example DSTL-8, Step a (X = F), (2S,2′S,5S,5′S)-*tert*-butyl 5,5′-(5,5′-

(biphenyl-4,4′-diyl)bis(4-fluoro-1H-imidazole-5,2-diyl))bis(2-methylpyrrolidine-1-carboxylate) (33 mg, 5.1 %) as a yellow-orange solid LC-MS (Cond.-D4): RT = 4.64 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}F_2N_6O_4$: 689.36; found 689.50. Example DSTL-8, Step a (X = H) (2S,5S)-*tert*-butyl 2-(5-(4′-(2-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-4-fluoro-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (108.6 mg, 17 %) as a yellow-orange solid. LC-MS (Cond.-D4): RT = 3.83 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}FN_6O_4$: 671.37; found 671.48 and recovered starting material (321.2 mg, 80%) as a reddish-orange solid.

Example DSTL-8, Step b



X = H
X = F

[00482] The products of Example DSTL-8, Step a, (X = F) and (X = H), were brought forward separately. Removal of the protecting groups was performed as described in the procedure from Example DSTL-1, Step h.

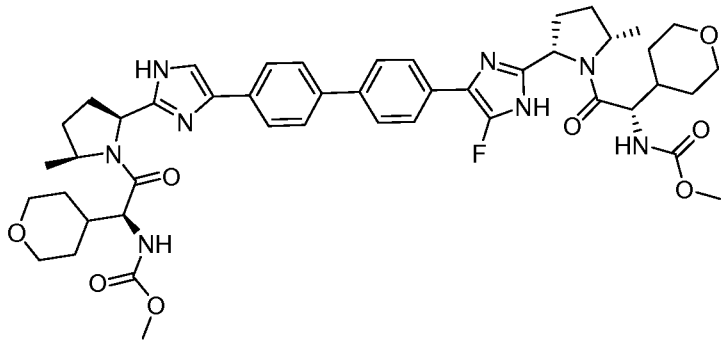
[00483] Example DTSL-8, Step b (X = F): Yellow solid, 22.7 mg; LC-MS (Cond.-D4): RT = 3.03 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{30}F_2N_6$: 489.26; found 489.35.

[00484] Example DTSL-8, Step b (X = H): 35 mg (95% pure); LC-MS (Cond.-D4): RT = 2.63 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{28}H_{31}FN_6$: 471.27; found 471.33.

Example DSTL-8

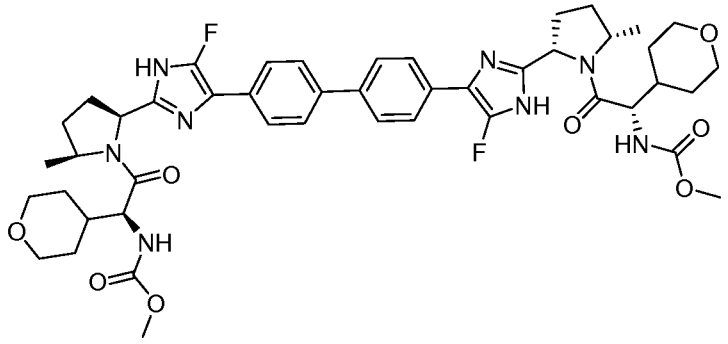
[00485] Example DSTL-5 was prepared from Example DSTL-8, Step b (X = H) according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC; 0% - 50%B over a 30 min gradient at 40ml/min using a Waters SunFire column (30 x 100 mm, S5) B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%TFA. There was isolated Example DSTL-8 (31.9 mg, 41%) as a light peach-colored solid. LC-MS (Cond.-D4): RT = 3.66 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{42}H_{54}FN_8O_6$: 785.42; found 785.48.

Example DSTL-9



[00486] Example DSTL-9 was prepared from Example DSTL-8, Step b (X = H) according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated Example DSTL-9 (27.2 mg, 32%) as a pale yellow solid. LC-MS (Cond.-D4): RT = 3.37 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{46}H_{58}FN_8O_8$: 869.44; found 869.54.

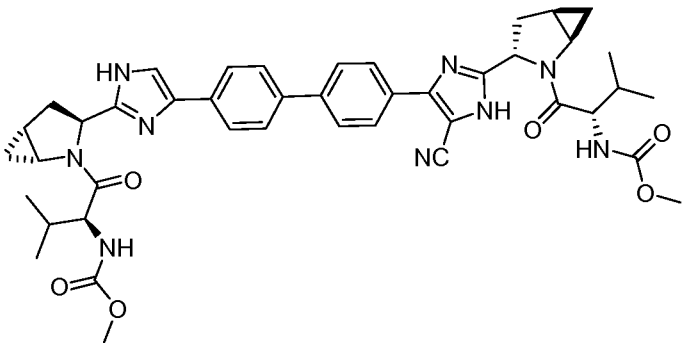
Example DSTL-10



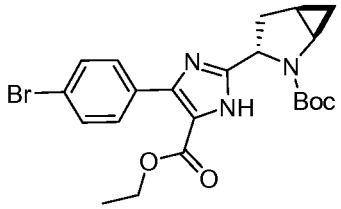
[00487] Example DSTL-10 was prepared from Example DSTL-8, Step b (X = F) according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA.

There was isolated Example DSTL-10 (13.8 mg, 25%) as a pale yellow solid. LC-MS (Cond.-D4): RT = 4.28 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}F_2N_8O_8$: 887.43; found 887.50.

Example DSTL-11

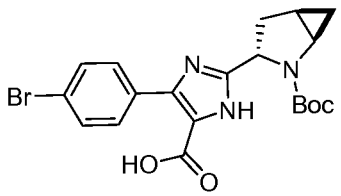


Example DSTL-11, Step a



[00488] The preparation of DSTL-11, Step a, was conducted in analogous fashion to compound J5 in patent application 20080213 US 10889A USCIP. LC-MS (Cond.-D4): RT = 2.22 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{22}H_{27}BrN_3O_4$: 476.12; found 478.17.

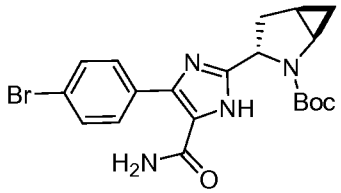
Example DSTL-11, Step b



[00489] 5N sodium hydroxide (1.469 mL, 7.4 mmol) was added to a solution of DSTL-11, Step a (1R,3S,5R)-*tert*-butyl 3-(4-(4-bromophenyl)-5-(ethoxycarbonyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.75 g, 3.7 mmol) in ethanol (40 mL). The mixture was stirred at 50 °C for 16 h and additional 5N NaOH (1.5 mL) was added. The mixture was stirred at 60 °C for 6h and additional 5N NaOH (0.75 mL)

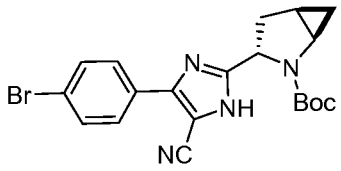
and stirring was continued at 60 °C for 16h. The ethanol was removed by rotary evaporation and the residue was taken up in ethyl acetate and neutralized to pH = 5 (1N HCl approx 20mL until close to pH = 7, then with pH =5 phosphate buffer). The organic layer was separated, washed with brine, dried and concentrated. There was isolated Example DSTL-11, Step b (1.6 g, 92 %) as a white solid. LC-MS (Cond.-D4): RT = 1.78 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{20}H_{22}BrN_3O_4$: 448.09; found 447.97.

Example DSTL-11, Step c



[00490] CDI (0.58 g, 3.57 mmol) was added in one portion to a stirred soln of DSTL-11, Step b, 4-(4-bromophenyl)-2-((1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazole-5-carboxylic acid (1.6 g, 3.57 mmol) in dry THF (30 mL). The mixture was stirred at 50 °C for 4 h before being cooled to rt and NH_4OH (conc) (4.96 mL, 35.7 mmol) was added. The mixture was stirred for 16 h before, diluted with EtOAc, washed with sat'd $NaHCO_3$ soln, brine, and dried. The crude product was charged to a Thompson 160 g silica gel cartridge and eluted 40 - 100% B over 3 L, followed by a hold at 100% B for 1L . (Solvent B = EtOAc; Solvent A = hexanes). There was isolated Example DSTL-11, Step c, (1.76 g 99%). LC-MS (Cond.-D4): RT = 1.75 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{20}H_{24}BrN_4O_3$ 449.10; found: 449.06.

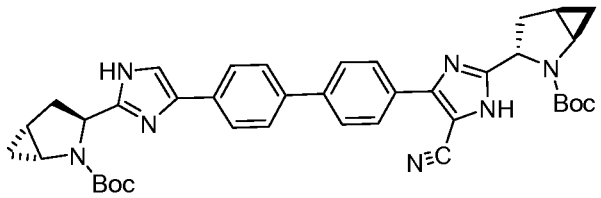
Example DSTL-11, Step d



[00491] 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) (168 mg, 0.91 mmol) was added in one portion to a stirred solution of Example DSTL-11, Step c, (1R,3S,5R)-*tert*-butyl 3-(4-(4-bromophenyl)-5-carbamoyl-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-

2-carboxylate (903 mg, 1.82 mmol) in dry DMF (4 mL). The mixture was stirred at for 2 h and then warmed to 50 °C for 16 h. Additional cyanuric chloride (20mg) was added and the mixture was stirred further at 50 °C for 24 h, diluted with EtOAc and water, and the organic layer was washed with sat'd $NaHCO_3$ soln, brine, and dried (Na_2SO_4). The crude product was charged to a Thompson 90 g silica gel cartridge and eluted 25-100% B over 1.5 L, followed by a hold at 100% B 500 mL. (Solvent B = EtOAc; Solvent A = hexanes). There was isolated Example DSTL-11, Step d, (346 g 60%) as a yellowish-tan foam. LC-MS (Cond.-D4): RT = 3.93 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{20}H_{22}BrN_4O_2$ 431.09; found: 431.01.

Example DSTL-11, Step e

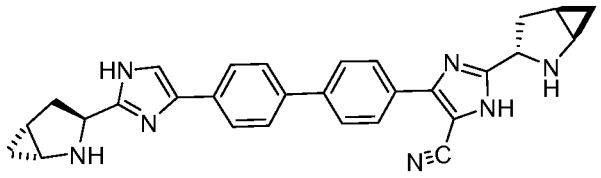


[00492] Tetrakis(triphenyl)palladium (45.8 mg, 0.04 mmol) was added to a argon purged suspension of Example DSTL-11, Step d, (1R,3S,5R)-*tert*-butyl 3-(5-(4-bromophenyl)-4-cyano-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (340 mg, 0.79 mmol). (1R,3S,5R)-*tert*-butyl 3-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (393 mg, 0.871 mmol), and $NaHCO_3$ (333 mg, 3.96 mmol) in DME (6 mL) and Water (1.5 mL) in a thick-walled, screw-topped tube. The reaction mixture was flushed with argon, sealed, and immersed in a pre-heated oil bath (80 °C) and stirred 14 h. The mixture was diluted with EtOAc, washed with sat'd $NaHCO_3$ soln, brine, dried over (Na_2SO_4). The crude product was charged to a Thompson 90 g silica gel cartridge and eluted with 35 – 100 % B over 1.5 L, followed by hold at 100 % B for 0.5 L. (Solvent B = EtOAc; Solvent A = hexanes). There was isolated Example DSTL-11, Step e, (200 mg, 36%) as a light yellow foam.

[00493] A small sample (~20 mg) was subject to further purification by prep. HPLC (0%B to 100%B over a 25 min gradient at 40ml/min) using a PHENOMENEX® Gemini column (30 x 100 mm, 10u) where Solvent B = 95% CH_3CN - 5% H_2O- 10mM NH_4OAc

and A = 5% CH_3CN - 95% H_2O - 10mM NH_4OAc. (12.9 mg) LC-MS (Cond.-D4): RT = 3.51 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{39}H_{44}N_7O_4$ 674.35; found: 674.29.

Example DSTL-11, Step f

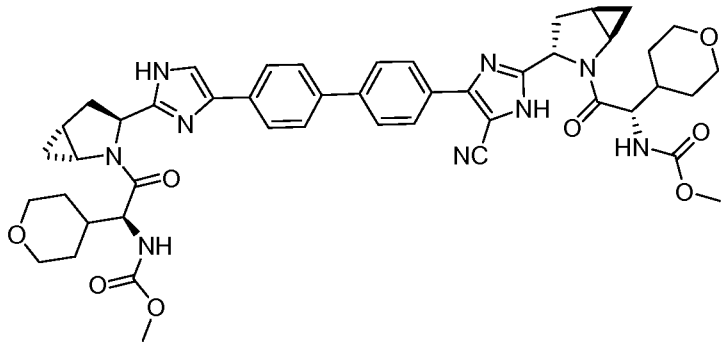


[00494] The product of Example DSTL-11, Step f was obtained upon removal of the protecting groups as described in the procedure from Example DSTL-1, Step h. LC-MS (Cond.-D4): RT = 2.36 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{29}H_{28}N_7$: 474.24; found 474.13.

Example DSTL-11

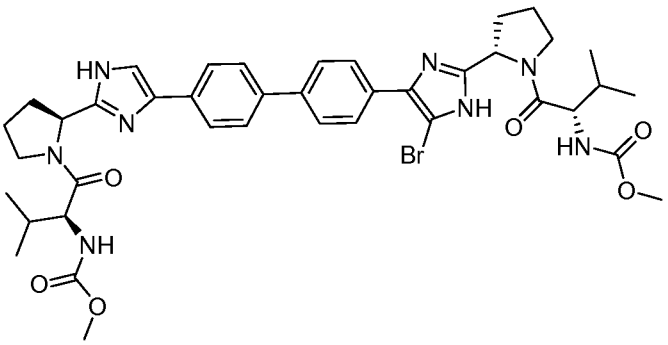
[00495] Example DSTL-11 was prepared from Example DSTL-11, Step f according to the procedure described for the preparation of Example GW2. Purification was accomplished by preparative HPLC; 0% - 50%B over a 30 min gradient at 40ml/min using a Waters SunFire column (30 x 100 mm, S5) B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1%TFA. There was isolated Example DSTL-11 (21.5 mg, 31%) as an off white solid. ^1H NMR (MeOD, 500 MHz, δ): 7.93-7.82 (m, 9 H), 5.15-5.08 (m, 2H), 4.58 – 4.56 (m, 2H), 3.82 (br. s. 1H), 3.72 (br. s, 1H) 3.67 (s, 6H), 2.73-2.67 (m, 1H), 2.50-2.46 (m, 3H), 2.21-2.14 (m, 2H), 2.09 (br. s, 1H), 2.03 (br. s, 1H), 1.14-1.10 (m, 2H), 1.05 – 1.02 (m, 6H), 0.97-0.93 (m, 6H), 0.90 (br. s, 1H), 0.83 (br. s, 1H). LC-MS (Cond.-D4): RT = 3.25 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_6$: 780.39; found 788.31.

Example DSTL-12

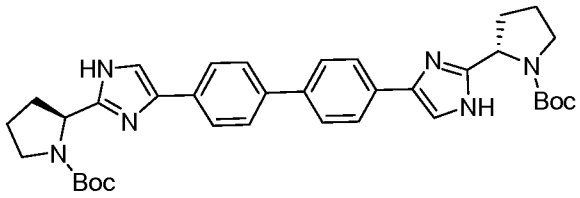


[00496] Example DSTL-12 was prepared from Example DSTL-11, Step f according to the procedure described for the preparation of Example GW2 except using (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid instead of Cap-51. Purification was accomplished by preparative HPLC (0 - 50% B) over a 25 min gradient (at 40ml/min) using a Waters SunFire column (30 x 100 mm, S5) where Solvent B = 90% CH_3CN - 10% H_2O - 0.1% TFA and A = 5% CH_3CN - 95% H_2O - 0.1% TFA. There was isolated Example DSTL-12 (26.7 mg, 35%) as an off white solid. LC-MS (Cond.-D4): RT = 2.98 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{47}H_{54}N_9O_8$: 872.41; found 872.35.

Example JLR-1

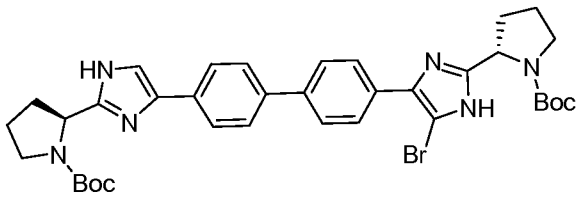


Example JLR-1, Step a



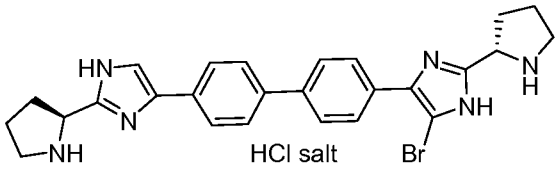
[00497] For the synthesis of Example JLR-1, Step a, see the process patent application WO 2009/020825.

Example JLR-1, Step b



[00498] A solution of a 1 M bromine in AcOH (0.4 mL) was added to a solution of Example JLR-1, Step a (250 mg, 0.40 mmol) in acetic acid (15 mL) and stirred for 3 h. The reaction mixture was poured onto DCM (100 mL) and treated with sat'd $NaHCO_3$ soln and solid $NaHCO_3$, until pH = neutral. The organic phase was concentrated and dried under vacuum. The reaction gave a 1:1:1 mixture of starting material : mono bromide: dibromide which were separated upon application (DCM) to a Thompson SiO_2 column (25 g). Elution (BIOTAGE®) by gradient 15 - 100% B over 500 mL gave Example JLR-1, Step b (180 mg). LC-MS (Cond.-J4): RT = 2.75 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}BrN_6O_4$: 705.26; found 705.22.

Example JLR-1, Step c



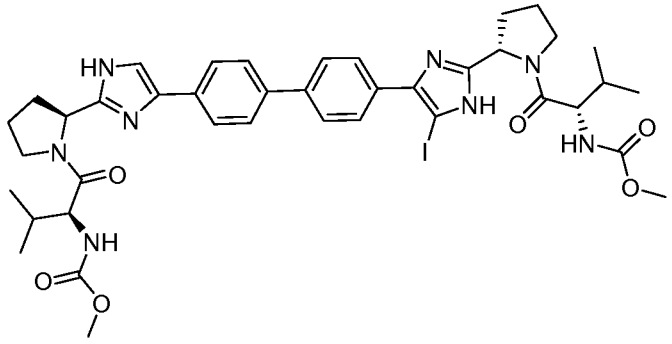
[00499] A solution of 4N HCl in dioxane (4 mL) was added to Example JLR-1, Step b (38 mg, 0.054 mmol) in MeOH (4 mL) and stirred for 4 h. The solvent was removed under vacuum and the tetra HCl salt was dried under high vacuum. LC-MS (Cond.-J4): RT = 1.75 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{26}H_{28}BrN_6$: 503.16; found 503.26.

Example JLR-1

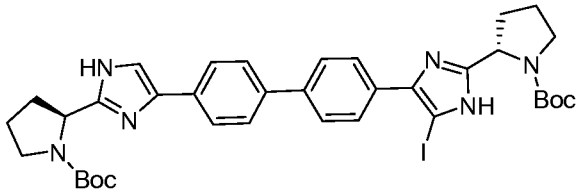
[00500] Example JLR-1 was prepared from Example JLR-1, Step c according to the procedure described for the preparation of Example GW2. Purification by preparative HPLC PHENOMENEX® Luna column (30 x 100 mm S10) running 25 min gradient from 15-100% B (at 40ml/min) where Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA

and A = 5% MeOH - 95% H_2O - 0.1% TFA. LC-MS (Cond.-J4): RT = 2.61 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{50}BrN_8O_6$: 819.31; found 819.23.

Example JLR-2

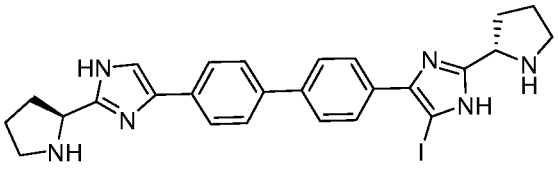


Example JLR-2, Step a



[00501] Iodine (162 mg, 0.640 mmol) was added to a solution of Example JLR-1, Step a (400 mg, 0.640 mmol) and $NaHCO_3$ (161 mg, 1.921 mmol) in dioxane (15 mL) and water (15 mL) and the reaction stirred for 6 h, quenched with 10% $Na_2S_2O_3$ solution (40 mL) and diluted with EtOAc/THF (2:1). The organic phase was concentrated and the crude product was applied (DCM) to a Thompson silica gel column (40 g) and eluted with 35-100% B over 1 L (A/B DCM/EtOAc) to give a mixture of starting material, diiodide (255 mg), and Example JLR-2, Step a (46 mg, 9%). LC-MS (Cond.-J4): RT = 2.45 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}IN_6O_4$: 751.24; found 751.18.

Example JLR-2, Step b



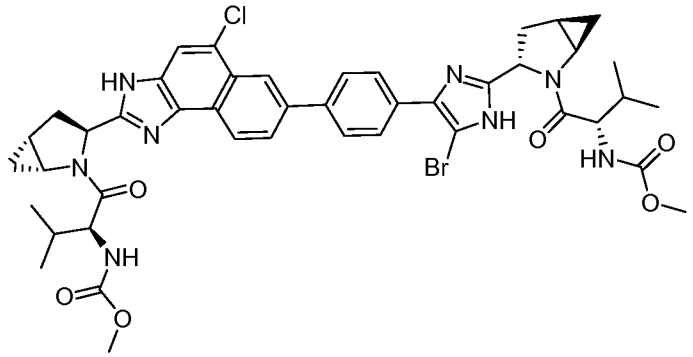
HCl salt

[00502] A solution of 4N HCl in dioxane (5 mL) was added to JLR-2, Step a (46 mg, 0.061 mmol) in MeOH (5 mL) and stirred for 4 h. The solvent was removed under vacuum and the tetra HCl salt was dried under high vacuum. LC-MS (Cond.-J4): RT = 1.70 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{26}H_{28}IN_6$: 551.13; found 551.09.

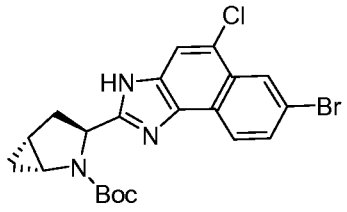
Example JLR-2

[00503] Example JLR-2 was prepared from Example JLR-2, Step b according to the procedure described for the preparation of Example GW2. Purification by semi-prep HPLC; Dynamax 6A semi-prep C8 column; 5% - 95% B over 30 min (at 20ml/min) where Solvent B = 90% CH_3CN - 10% H_2O - 1% NH_4OAc and A = 5% CH_3CN - 95% H_2O - 1% NH_4OAc. LC-MS (Cond.-J4): RT = 2.35 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{50}IN_8O_6$: 865.29; found 865.31.

Example JLR-3



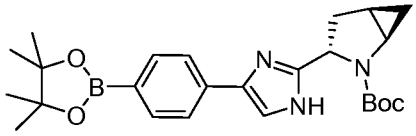
Example JLR-3, Step a



[00504] NCS (175 mg, 1.310 mmol) was added to a solution of Example DSTL-1, Step d (510 mg, 1.191 mmol) in DMF (10 mL) and stirred for 18 h at 50 °C. The solvent was removed by rotary evaporation under high vacuum, and the residue charged (DCM) to a Thomson silica gel cartridge (80 g). Gradient elution was performed from 25 - 100% B over 750 mL (A/B Hex/EtOAc) to give Example JLR-3, Step a (250 mg, 46%). ^1H NMR

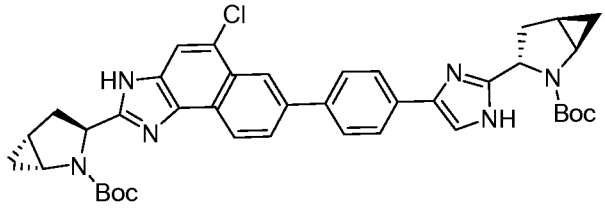
(MeOD, 500 MHz, δ): 8.58 (s, 1H), 8.39 (d, J = 8.6 Hz, 1H), 7.97 (s. 1H), 7.93 (d, J = 7.6 Hz, 1H), 4.98 (s, 1H), 3.70 (s, 1 H), 2.76-2.71 (m, 1H), 2.50-2.45 (m, 1H), 1.86 (s, 1H), 1.48/1.12 (s, 9H), 0.96-0.92 (m, 1H), 0.79-0.77 (m, 1H). LC-MS (Cond.-J4): RT = 3.13 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrClN_3O_2$: 464.06; found 464.05.

Example JLR-3, Step a.1



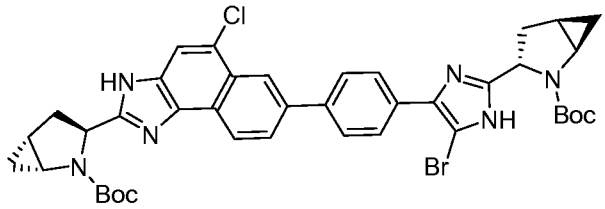
[00505] Example JLR-3, Step a.1 was prepared from Example DSTL-1, Step d.1 according to a procedure described in patent application WO 2008/021927 for the preparation of its desmethano analog.

Example JLR-3, Step b



[00506] Example JLR-3, Step b was prepared from Example JLR-3, Step a and Example JLR-3, Step a.1 according to the procedure described for the preparation Example DSTL-1, Step g to give Example JLR-3, Step b. LC-MS (Cond.-J4): RT = 2.72 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}ClN_6O_4$: 707.31; found 707.44.

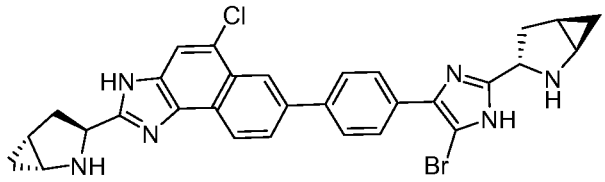
Example JLR-3, Step c



[00507] Example JLR-3, Step c was prepared from Example JLR-3, Step b according to the procedure described for the preparation DSTL-3, Step a to give Example JLR-3,

Step c. LC-MS (Cond.-J4): RT = 3.30 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}BrClN_6O_4$: 787.21; found 787.34.

Example JLR-3, Step d



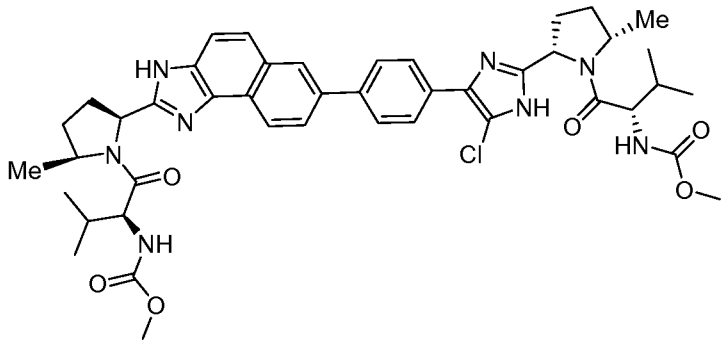
HCl salt

[00508] Example JLR-3, Step d was prepared from Example JLR-3, Step c according to the procedure described in the procedure from Example JLR-1, Step b. LC-MS (Cond.-J4): RT = 2.37 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{30}H_{27}BrClN_6$: 587.12; found 587.14.

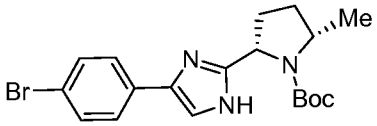
Example JLR-3

[00509] Example JLR-3 was prepared from Example JLR-3, Step d according to the procedure described for the preparation of Example GW2. Purification by preparative HPLC PHENOMENEX® Luna column (30 x 100 mm S10) running 18 min gradient from 15-100% B (at 40ml/min) where Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA and A = 5% MeOH - 95% H_2O - 0.1% TFA. ^1H NMR (MeOD, 500 MHz, δ): 8.69-8.68 (m, 1H), 8.52-8.50 (m, 1H), 8.18-8.16 (m, 1H), 7.98-7.96 (m. 1H), 7.91-7.90 (m, 4H), 5.34-5.34 (m, 1H), 5.09-5.06 (m, 1 H), 4.62-4.58 (m, 2H), 3.91 (br s, 1H), 3.76 (br s, 1H) 3.69 (s, 6H), 2.77-2.73 (m, 1H), 2.64-2.59 (m,, 1H), 2.51-2.48 (m, 2H), 2.23-2.16 (m, 3H), 2.06 (br s, 1H), 1.17-1.12 (m, 2H), 1.06-0.92 (m, 13H), 0.83 (m, 1H). LC-MS (Cond.-J4): RT = 3.14 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_4BrClN_8O_6$: 901.27; found 901.45.

Example JLR-4

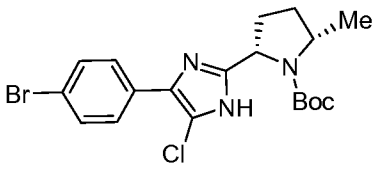


Example JLR-4, Step a



[00510] Hunig's base (1.2 g, 9 mmol) was added to a solution of 2-bromo-1-(4-bromophenyl)ethanone (2.5 g, 8.99 mmol) and (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (1.9 g, 8.29 mmol) in acetonitrile (75 mL) and stirred for 6 h at 24 °C. The reaction mixture was concentrated and the residue taken up in EtOAc and washed with water. Concentration gave a white solid which was taken up in xylene (90 mL). Ammonium acetate (4.23 g, 70.4 mmol) was added, and the solution was stirred in a screw-capped pressure vessel at 135 °C for 3.5 h. The reaction mixture was diluted with EtOAc (400 mL) and washed with sat'd $NaHCO_3$ soln and concentrated. The crude product was charged (DCM) to a 80g Thompson silica gel cartridge and gradient elution was performed from 15% to 100% B over 1 L (A/B Hex/EtOAc) gave Example JLR-4, Step a (yield not determined). LC-MS (Cond.-J4): RT = 2.21 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$: 406.12; found 406.10. [Note: for the synthesis of the starting carboxylic acid, see U.S. Patent Application 2009/0068140).

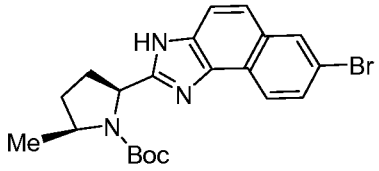
Example JLR-4, Step b



[00511] NCS (161 mg, 1.21 mmol) was added to a solution of Example JLR-4, Step a (700 mg, 1.7 mmol) in DMF (10 mL) and stirred for 18 h at 50 °C. Additional NCS (50

mg) and the reaction continued for 6 h before removing the solvent by nitrogen purge. The crude product was charged (DCM) to a 40g Thompson silica gel cartridge, and gradient elution was performed from 15% to 100% B over 750 mL (A/B Hex/EtOAc) to give Example JLR-4, Step b (580 mg, 70 %). ^{1}H NMR (MeOD, 500 MHz, δ): 7.62 (appr s, 4H), 4.77 (br. s, 1H), 4.03 (br. s, 1H), 2.24 (br s, 2H), 2.16-2.11 (m, 1H) 1.79 (br. s, 1H), 1.47-1.25 (m, 12H). LC-MS (Cond.-J4): RT = 3.33 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{19}H_{24}BrClN_3O_2$: 440.08; found 440.0.

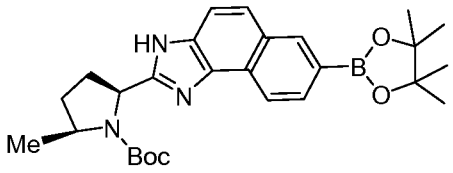
Example JLR-4, Step c



[00512] EEDQ (1.67 g, 6.75 mmol) was added to a solution of Example DSTL-1, Step c (1.6 g, 6.75 mmol) and (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (1.55 g, 6.75 mmol) in DCM (100 mL) and stirred for 6h. (Note: The dianiline was not completely soluble). The reaction mixture was diluted with DCM (1 vol) and washed with half sat'd $NaHCO_3$ soln. Concentration gave a solid (2.5 g). LC-MS (Cond.-J4): RT = 3.07 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{27}BrN_3O_3$: 448.13; found 448.11.

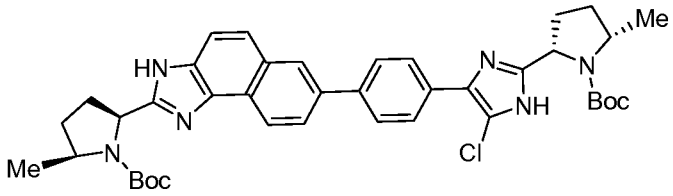
[00513] The crude solid (2.5 g, 5.58 mmol) was taken up in AcOH (200 mL) and stirred for 18 h at 60 °C. Concentration under high vacuum removed the solvent. The residue was taken up in DCM, washed with sat'd $NaHCO_3$ soln, and concentrated. The residue was charged (DCM) to a 80 g Thompson silica gel cartridge and gradient elution was performed from 15% to 100% B over 750 mL. (A/B Hex/EtOAc) to give Example JLR-4, Step c (2.6 g). ^{1}H NMR (MeOD, 500 MHz, δ): 8.36-8.35 (m, 2H), 8.0 (d, J = 9Hz, 1H), 7.91 (dd, J = 9, 2 Hz, 1H), 7.87 (d, J = 9 Hz, 1H), 5.31-5.28 (m, 1H), 4.17 (br. s, 1H), 2.59-2.56 (m, 1H), 2.39-2.31 (m, 2H) 1.86-1.83 (m, 1H), 1.52-1.19 (m, 12H). LC-MS (Cond.-J4): RT = 2.57 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430.12; found 430.09.

Example JLR-4, Step d



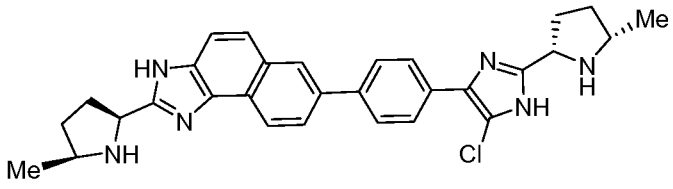
[00514] Example JLR-4, Step d was prepared from Example JLR-4, Step c according to the procedure described for the preparation of Example DSTL-1 Step f. LC-MS (Cond.-J4): RT = 2.86 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{27}H_{37}BN_3O_4$: 478.29; found 478.25.

Example JLR-4, Step e



[00515] Example JLR-4, Step e was prepared from Example JLR-4, Step d and Example JLR-4, Step b according to the procedure described for the preparation DSTL-1, Step g to give Example JLR-4, Step e. ^{1}H NMR (MeOD, 500 MHz, δ): 8.53 (d, J = 8.6 Hz, 1H), 8.49 (s, 1H), 8.20 (dd, J = 8.6, 2 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.9 Hz, 1H). 5.32 (t, J = 6.4 Hz, 1H), 4.85 (br. s, 1H), 4.20 (br. s, 1H), 4.06 (br. s, 1H). 2.59-2.58 (m, 1H), 2.44-2.28 (m, 4H), 2.19-2.15 (m, 1H). 1.89-1.84 (m, 1H), 1.83-1.79 (m, 1H), 1.54-1.20 (m, 24H). LC-MS (Cond.-J4): RT = 3.18 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{40}H_{48}ClN_6O_4$: 711.34; found 711.31.

Example JLR-4, Step f



HCl salt

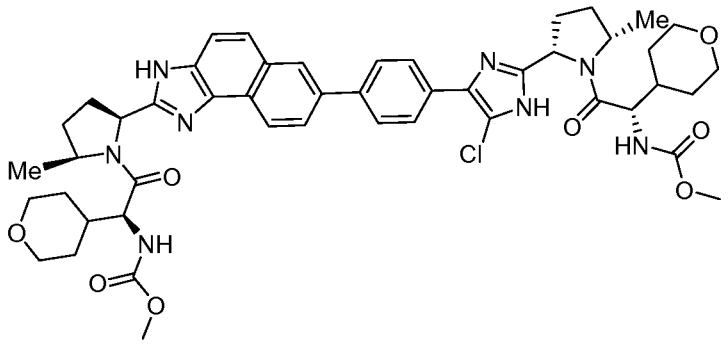
[00516] Example JLR-4, Step f was prepared from Example JLR-4, Step e according to the procedure described for the preparation Example JLR-1, Step b to give Example

JLR-4, Step f. LC-MS (Cond.-J4): RT = 2.19 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{30}H_{32}ClN_6$: 511.24; found 711.23.

Example JLR-4

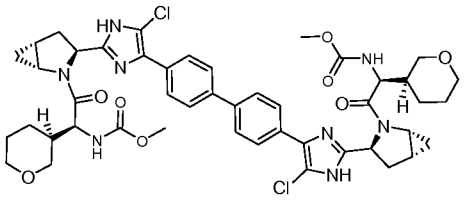
[00517] Example JLR-4 was prepared from Example JLR-4, Step f according to the procedure described for the preparation of Example GW2. Purification by preparative HPLC Luna Axia column (30 x 100 mm C18) running 25 min gradient from 15-100% B (at 40ml/min) where Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA and A = 5% MeOH - 95% H_2O - 0.1% TFA. LC-MS (Cond.-J4): RT = 3.12 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{44}H_{54}ClN_8O_6$: 825.39; found 825.31.

Example JLR-5

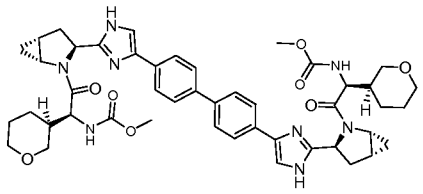


[00518] Example JLR-5 was prepared from Example JLR-4, Step f according to the procedure described for the preparation of Example GW2 except using and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid. Purification by preparative HPLC Luna Axia column (30 x 100 mm C18) running 25 min gradient from 15-100% B (at 40ml/min) where Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA and A = 5% MeOH - 95% H_2O - 0.1% TFA. LC-MS (Cond.-J4): RT = 2.85 min. LC-MS Anal. Calcd. for $[M+H]^+$ $C_{48}H_{58}ClN_8O_6$: 909.41; found 909.39.

Example ZY1



Example ZY1, Step a



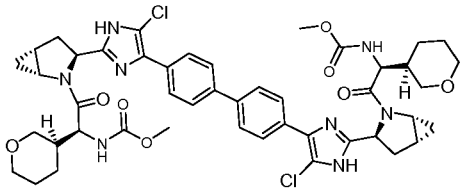
[00519] HATU (151 mg, 0.40 mmol) was added to a solution of an HCl salt of 4,4′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)biphenyl (Example 1e) (107 mg, 0.18 mmol) and (S)-2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetic acid (cap-177a) (86 mg, 0.40 mmol) in DMF (1.5 mL) and DIPEA (0.25 mL, 1.4 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (S,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (148.5 mg) as light yellow solid. LC-MS retention time =1.61 min; m/z = 847 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water :90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.80 - 7.91 (m, 10 H), 5.13 (dd, *J*=9.3, 7.0 Hz, 2 H), 4.79 (d, *J*=8.3 Hz, 2 H), 3.84 - 3.97 (m, 2 H), 3.70 - 3.80 (m, 4 H), 3.68 (s, 6 H), 3.52 – 3.63 (m, 2 H), 3.34 - 3.42 (m, 2 H), 2.61 – 2.75 (m, 2 H), 2.43 - 2.54 (m, 2 H), 1.98 - 2.15 (m, 4 H), 1.67 – 1.84 (m, 4 H), 1.48 - 1.65 (m, 4 H), 0.98 - 1.16 (m, 2 H), 0.77 - 0.93 (m, 2 H).

Example ZY1

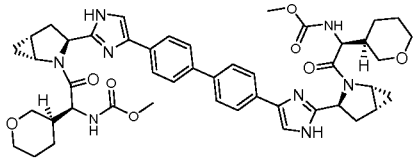
[00520] NCS (8.2 mg, 0.061 mmol) was added to a solution of a TFA salt of dimethyl (S,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY1, Step a) (33 mg, 0.031 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. The reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (S,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-

4,4′-diyl)bis(5-chloro-1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate, (Example ZY1) (25 mg) as white solid. LC-MS retention time = 1.92 min; m/z = 458 $[M/2+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% Water/ 5% Methanol/10 mM Ammonium Acetate. Solvent B = 5% Water/ 95% Methanol/10 mM Ammonium Acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.77 - 7.85 (m, 8 H), 5.03 (dd, *J*=8.8, 6.0 Hz, 2 H), 4.75 – 4.86 (m, 2 H), 3.71 - 3.89 (m, 6 H), 3.67 (s, 6 H), 3.36 - 3.62 (m, 4 H), 2.38 - 2.57 (m, 4 H), 1.94 - 2.12 (m, 4 H), 1.69 - 1.87 (m, 4 H), 1.46 - 1.65 (m, 4 H), 1.03 - 1.17 (m, 2 H), 0.77 - 0.85 (m, 2 H).

Example ZY2



Example ZY2, Step a



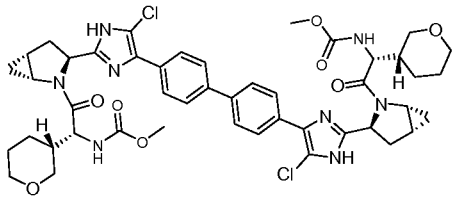
[00521] HATU (140 mg, 0.37 mmol) was added to a solution of an HCl salt of 4,4′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)biphenyl, (Example 1e) (100 mg, 0.17 mmol) and (S)-2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetic acid (cap117b) (80 mg, 0.37 mmol) in DMF (1.5 mL) and DIPEA (0.23 mL, 1.3 mmol) and the mixture was stirred at rt for 3 h. Then the reaction mixture was diluted with MeOH and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (R,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY2, Step a) (76.2 mg) as white solid. LC-MS retention time =1.53 min; m/z = 847 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10%

Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.75 - 7.96 (m, 10 H), 5.13 (dd, *J*=9.3, 7.0 Hz, 2 H), 4.60 (d, *J*=8.3 Hz, 2 H), 3.77 - 3.95 (m, 6 H), 3.67 (s, 6 H), 3.24 - 3.47 (m, 4 H), 2.62 - 2.76 (m, 2 H), 2.40 - 2.57 (m, 2 H), 1.97 - 2.19 (m, 4 H), 1.54 - 1.82 (m, 6 H), 1.36 - 1.54 (m, 2 H), 1.00 - 1.17 (m, 2 H), 0.79 - 0.93 (m, 2 H).

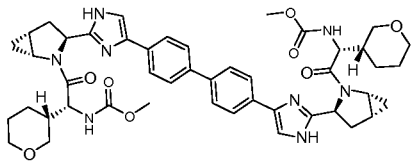
Example ZY2

[00522] NCS (5.2 mg, 0.039 mmol) was added to a solution of a TFA salt of dimethyl (R,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY2, Step a) (21 mg, 0.020 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (R,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(5-chloro-1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY2) (10.8 mg) as white solid. LC-MS retention time = 1.92 min; m/z = 458 $[M/2 + H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% Water/ 5% Methanol/10 mM Ammonium Acetate. Solvent B = 5% Water/ 95% Methanol/10 mM Ammonium Acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.76 - 7.87 (m, 8 H), 5.04 (dd, *J*=8.8, 6.0 Hz, 2 H), 4.61 (d, *J*=8.3 Hz, 2 H), 3.75 - 3.95 (m, 6 H), 3.66 (s, 6 H), 3.35 - 3.48 (m, 4 H), 2.39 - 2.58 (m, 4 H), 1.97 - 2.16 (m, 4 H), 1.73 - 1.87 (m, 2 H), 1.40 - 1.73 (m, 6 H), 1.01 - 1.16 (m, 2 H), 0.81 (d, *J*=1.8 Hz, 2 H).

Example ZY3



Example ZY3, Step a



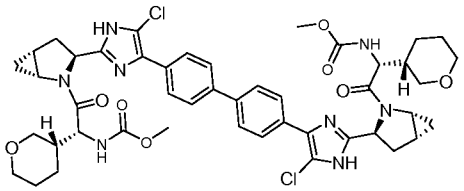
[00523] HATU (82 mg, 0.22 mmol) was added to a solution of an HCl salt of 4,4′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)biphenyl (Example 1e) (58.3 mg, 0.098 mmol) and (R)-2-(methoxycarbonylamino)-2-((R)-tetrahydro-2H-pyran-3-yl)acetic acid (cap 117c) (49 mg, 0.23 mmol) in DMF (1 mL) and DIPEA (0.14 mL, 0.79 mmol) and the mixture was stirred at rt for 3 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (R,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY3, Step a) (79.8 mg) as white solid. LC-MS retention time = 1.63 min; m/z = 847 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

Example ZY3

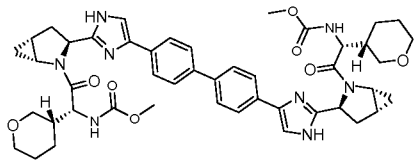
[00524] NCS (6.7 mg, 0.050 mmol) was added to a solution of a TFA salt of dimethyl (R,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY3, Step a) (27 mg, 0.025 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (R,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(5-chloro-1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY3) (15.8 mg) as white solid. LC-MS retention time = 1.93 min; m/z = 458 $[M/2 + H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% Water/ 5% Methanol/10 mM Ammonium Acetate. Solvent B = 5% Water/ 95%

Methanol/10 mM Ammonium Acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220).

Example ZY4



Example ZY4, Step a



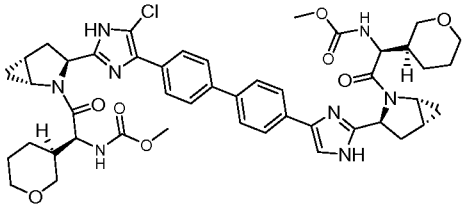
[00525] HATU (75 mg, 0.20 mmol) was added to a solution of an HCl salt of 4,4′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)biphenyl (Example 1e) (53.5 mg, 0.090 mmol) and (R)-2-(methoxycarbonylamino)-2-((S)-tetrahydro-2H-pyran-3-yl)acetic acid (cap117d) (45 mg, 0.21 mmol) in DMF (1 mL) and DIPEA (0.13 mL, 0.72 mmol) and the mixture was stirred at rt for 3 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (S,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY4, Step a) (78.5 mg) as white solid. LC-MS retention time = 1.57 min; m/z = 847 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water :90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220).

Example ZY4

[00526] NCS (9.2 mg, 0.069 mmol) was added to a solution of a TFA salt of dimethyl (S,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-

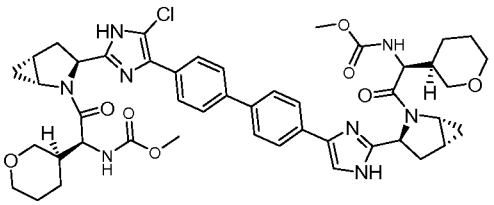
3-yl)ethane-2,1-diyl)dicarbamate (Example ZY4, Step a) (37 mg, 0.034 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (S,1R,1′R)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(5-chloro-1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY4) (25 mg) as white solid. LC-MS retention time = 1.93 min; m/z = 458 $[M/2 + H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 95% Water/ 5% Methanol/10 mM Ammonium Acetate. Solvent B = 5% Water/ 95% Methanol/10 mM Ammonium Acetate. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 2 min. Wavelength = 220).

Example ZY5



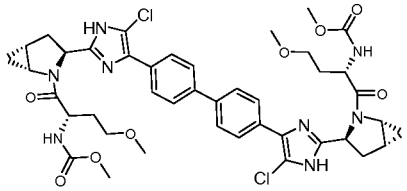
[00527] NCS (5.3 mg, 0.039 mmol) was added to a solution of a TFA salt of dimethyl (S,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((S)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY1, Step a) (42.4 mg, 0.039 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. Then the reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield Example ZY5 as a TFA salt (11.7 mg, white solid). LC-MS retention time = 2.04 min; m/z = 881 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 7.76 - 7.92 (m, 9 H), 5.13 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.04 (dd, *J*=8.0, 6.5 Hz, 1 H), 4.74 - 4.80 (m, 2 H), 3.71 - 3.94 (m, 6 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.36 - 3.63 (m, 4 H), 2.63 - 2.75 (m, 1 H), 2.40 - 2.55 (m, 3 H), 1.95 - 2.15 (m, 4 H), 1.67 - 1.86 (m, 4 H), 1.45 - 1.65 (m, 4 H), 1.03 - 1.18 (m, 2 H), 0.84 - 0.91 (m, 1 H), 0.75 - 0.83 (m, 1 H).

Example ZY6

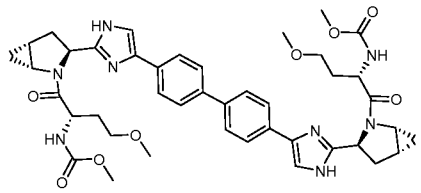


[00528] NCS (1.1 mg, 8.4 μmol) was added to a solution of a TFA salt of dimethyl (R,1S,1′S)-2,2′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(2-oxo-1-((R)-tetrahydro-2H-pyran-3-yl)ethane-2,1-diyl)dicarbamate (Example ZY2, Step a) (8.1 mg, 8.4 μmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. Then the reaction was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of Example ZY6 (2.2 mg) as white solid. LC-MS retention time = 2.01 min; m/z = 881 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^1H NMR (400 MHz, MeOD) δ ppm 7.77 - 7.90 (m, 9 H), 5.12 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.05 (dd, *J*=7.9, 6.1 Hz, 1 H), 4.58 - 4.96 (m, 2 H), 3.71 - 3.94 (m, 6 H), 3.68 (s, 3 H), 3.66 (br. s., 3 H), 3.34 - 3.46 (m, 4 H), 2.64 - 2.75 (m, 1 H), 2.40 - 2.54 (m, 3 H), 1.96 - 2.16 (m, 4 H), 1.40 - 1.85 (m, 8 H), 1.04 - 1.18 (m, 2 H), 0.84 - 0.92 (m, 1 H), 0.79 (m, 1 H).

Example ZY7



Example ZY7, Step a



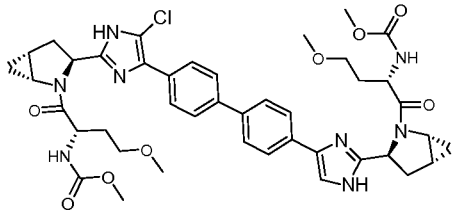
[00529] HATU (95 mg, 0.25 mmol) was added to a solution of an HCl salt of 4,4′-bis(2-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-4-yl)biphenyl (Example 1e) (67.6 mg, 0.114 mmol) and (S)-4-methoxy-2-(methoxycarbonylamino)butanoic acid (Example ZY7, Step a) (50 mg, 0.26 mmol) in DMF (1 mL) and DIPEA (0.16 mL, 0.91 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2′S)-1,1′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(4-methoxy-1-oxobutane-2,1-diyl)dicarbamate (Example ZY7, Step a) (96.4 mg) as white solid. LC-MS retention time = 1.53 min; m/z 795 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.78 - 7.97 (m, 10 H), 5.16 (dd, *J*=9.2, 6.7 Hz, 2 H), 4.76 - 4.83 (m, 2 H), 3.75 - 3.84 (m, 2 H), 3.66 (s, 6 H), 3.45 - 3.56 (m, 4 H), 3.32 (s, 6 H), 2.68 (dd, *J*=13.4, 9.4 Hz, 2 H), 2.42 - 2.53 (m, 2 H), 2.01 - 2.23 (m, 4 H), 1.80 - 1.95 (m, 2 H), 1.05 - 1.18 (m, 2 H), 0.78 – 0.98 (m, 2 H).

Example ZY7

[00530] NCS (9.7 mg, 0.073 mmol) was added to a solution of a TFA salt of dimethyl (2S,2′S)-1,1′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(4-methoxy-1-oxobutane-2,1-diyl)dicarbamate (Example ZY7, Step a) (29 mg, 0.036 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. The reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of dimethyl (2S,2′S)-1,1′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(5-chloro-1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(4-methoxy-1-oxobutane-2,1-diyl)dicarbamate (Example ZY7) (7.9 mg) as white solid. LC-MS

retention time = 2.51 min; m/z = 863 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.82 (s, 8 H), 5.07 (dd, *J*=8.5, 5.8 Hz, 2 H), 4.75 - 4.83 (m, 2 H), 3.70 - 3.76 (m, 2 H), 3.66 (s, 6 H), 3.44 - 3.54 (m, 4 H), 3.32 (s, 6 H), 2.39 - 2.57 (m, 4 H), 1.98 - 2.21 (m, 4 H), 1.82 - 1.94 (m, 2 H), 1.05 - 1.19 (m, 2 H), 0.78 - 0.92 (m, 2 H).

Example ZY8



[00531] NCS (5.6 mg, 0.042 mmol) was added to a solution of a TFA salt of dimethyl (2S,2′S)-1,1′-((1R,1′R,3S,3′S,5R,5′R)-3,3′-(4,4′-(biphenyl-4,4′-diyl)bis(1H-imidazole-4,2-diyl))bis(2-azabicyclo[3.1.0]hexane-3,2-diyl))bis(4-methoxy-1-oxobutane-2,1-diyl)dicarbamate (Example ZY7, Step b) (33.3 mg, 0.042 mmol) in DMF (1 mL) and the mixture was stirred at 50 °C for 16 h. The reaction mixture was diluted with MeOH, filtered and purified by prep HPLC (H_2O-MeOH with 0.1% TFA buffer) to yield a TFA salt of Example ZY8 (9.4 mg) as a white solid. LC-MS retention time = 1.99 min; m/z = 829 $[M+H]^+$. (Column: PHENOMENEX® Luna 3.0 x 50mm S10. Solvent A = 90% Water:10% Methanol: 0.1% TFA. Solvent B = 10% Water:90% Methanol: 0.1% TFA. Flow Rate = 4 mL/min. Start % B = 0. Final % B = 100. Gradient Time = 3 min. Wavelength = 220). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.77 - 7.91 (m, 9 H), 5.15 (dd, *J*=9.2, 6.7 Hz, 1 H), 5.07 (t, *J*=7.0 Hz, 1 H), 4.77 - 4.83 (m, 2 H), 3.76 - 3.83 (m, 1 H), 3.68 - 3.75 (m, 1 H), 3.66 (s, 6 H), 3.44 - 3.56 (m, 4 H), 3.33 (s, 6 H), 2.63 - 2.75 (m, 1 H), 2.41 - 2.56 (m, 3 H), 1.97 - 2.23 (m, 4 H), 1.80 - 1.95 (m, 2 H), 1.06 - 1.19 (m, 2 H), 0.87 - 0.96 (m, 1 H), 0.84 (m, 1 H).

BIOLOGICAL ACTIVITY

[00532] An HCV Replicon assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned

PCT/US2006/022197 and in O'Boyle et al., *Antimicrob. Agents Chemother.*, 49(4):1346-1353 (Apr. 2005). Assay methods incorporating luciferase reporters have also been used as described (Apath.com).

[00533] HCV-neo replicon cells and replicon cells containing resistance substitutions in the NS5A region were used to test the currently described family of compounds. The compounds were determined to have differing degrees of reduced inhibitory activity on cells containing mutations vs. the corresponding inhibitory potency against wild-type cells. Thus, the compounds of the present disclosure can be effective in inhibiting the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO 04/014852. It should be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC_{50} (Effective 50% inhibitory concentration) values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment, compounds of the present disclosure are inhibitory versus 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC_{50} values against HCV 1b are as follows. EC_{50} values against HCV 1b are as follows: A = 0.2 pM -<1 pM; B = 1 pM - <10 pM; and C = 10 pM -< 100 pM; and D = 100 pM-0.15 μM.

[00534] The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

Table 2

Example	EC_{50} (μM)	EC_{50}-Range
M1		B
M2		B
M4		B
M5		B
M6	4.08E-06	B
M7	2.13E-06	B
V1		B

Example	EC_{50} (μM)	EC_{50}-Range
V2	8.88E-05	C
V3		B
V4	3.22E-05	C
V5	6.58E-07	A
V5.1	3.90E-06	B
V5.2	3.06E-05	C
V5.3	1.33E-04	D
V6		A
V7		B
V8		B
V9	2.70E-06	B
V10		B
V11		B
V12		B
V13		B
V14		B
V15		C
V16	9.66E-07	A
GW1-1		B
GW1-2		B
GW1-3		B
GW2		B
GW2-1	1.27E-05	C
GW3		B
GW4		C
GW5		B
GW6		B
GW7		B
GW8		B
GW9		A

Example	EC_{50} (μM)	EC_{50}-Range
GW10		B
GW11		A
GW12		A
OL1	3.06E-06	B
OL2		B
OL3		B
OL4		B
OL5		B
OL6		B
OL7		B
OL8	2.09E-04	D
OL9	6.08E-06	B
OL10		D
OL11		B
OL12		C
OL13		B
OL14		C
OL15		B
OL16		C
OL17		B
OL18		B
OL19		C
OL20		D
OL21		C
OL22	4.08E-04	D
OL23		D
OL24		B
OL25		D
DSTL-1		A
DSTL-2		C

Example	EC_{50} (μM)	EC_{50}-Range
DSTL-3	1.25E-06	B
DSTL-4		A
DSTL-5	5.59E-07	A
DSTL-6		B
DSTL-7		B
DSTL-8		A
DSTL-9		B
DSTL-10		B
DSTL-11		A
DSTL-12		C
JLR-1		B
JLR-2		B
JLR-3		A
JLR-4	7.69E-07	A
JLR-5		B
ZY1		B
ZY2		B
ZY3		B
ZY4		B
ZY5		B
ZY6	1.08E-05	C
ZY7		B
ZY8		B

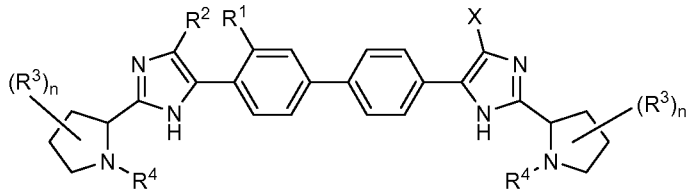
[00535] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and

all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

X is selected from hydrogen, alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl;

R^1 is selected from hydrogen and halo;

R^2 is selected from hydrogen, alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl; or

R^1 and R^2, together with the carbon atoms to which they are attached, form a six-membered aromatic ring optionally substituted with one halo group;

provided that at least one of X and R^2 is selected from alkenyl, cyano, cycloalkyl, (cycloalkyl)alkyl, halo, and heterocyclyl;

each R^3 is alkyl, wherein the alkyl can optionally form a fused three- or four-membered ring with an adjacent carbon atom or a spirocyclic three- or four-membered ring with the carbon atom to which it is attached; wherein the fused and spirocyclic rings are optionally substituted with one or two alkyl groups;

each R^4 is independently selected from hydrogen and $-C(O)R^5$; and

each R^5 is independently selected from alkoxy, alkyl, arylalkoxy, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, (NR^cR^d)alkenyl, and (NR^cR^d)alkyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently selected from alkoxy, heterocyclyl, and (NR^cR^d)alkyl.

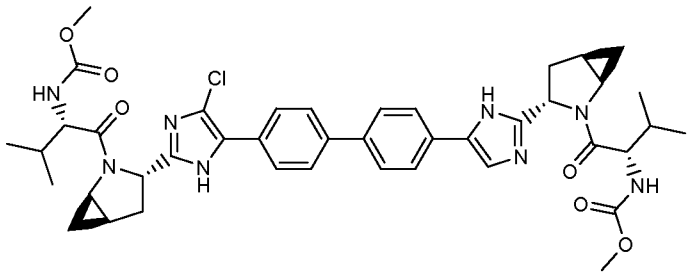
3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is halo.

4. A compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is halo.

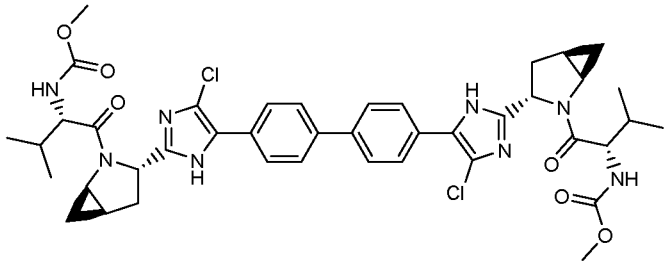
5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the carbon atoms to which they are attached, form a six-membered aromatic ring optionally substituted with one halo group.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is hydrogen.

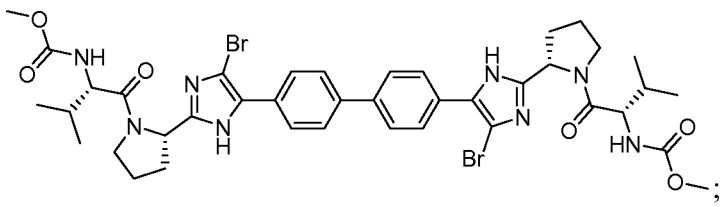
7. A compound selected from:



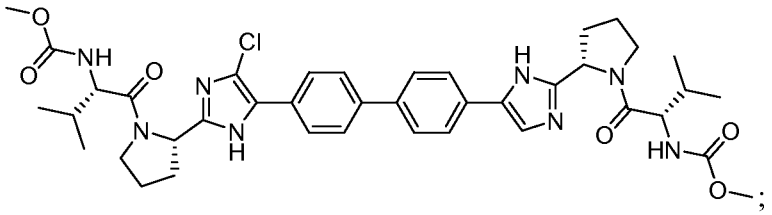
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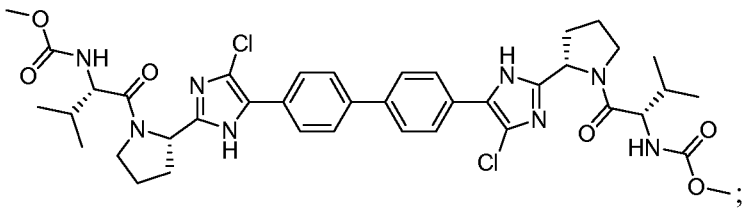


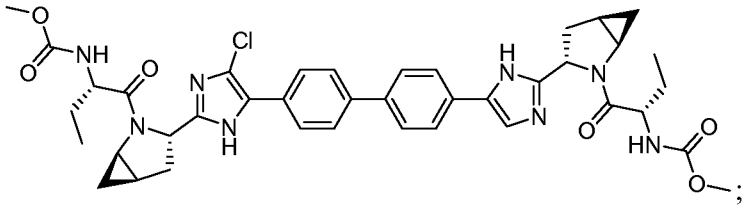
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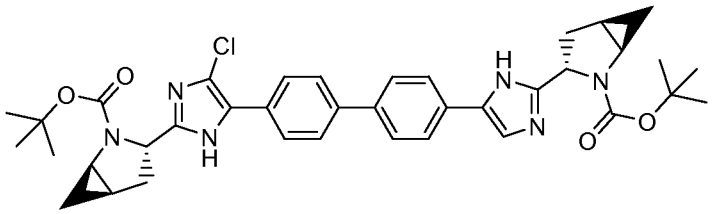


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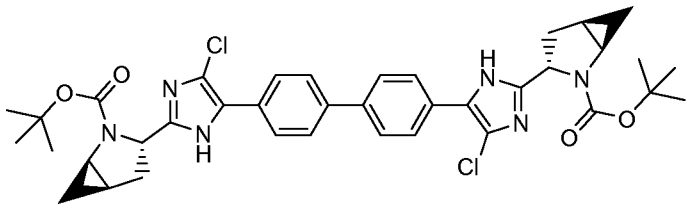




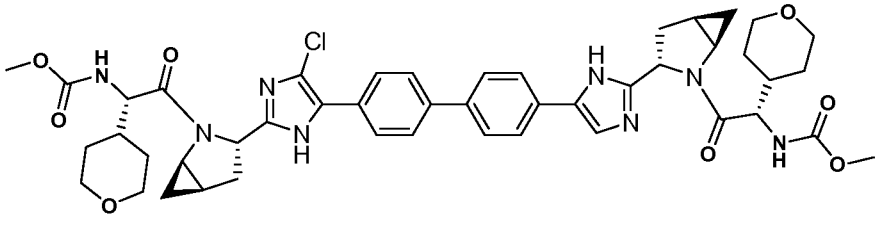




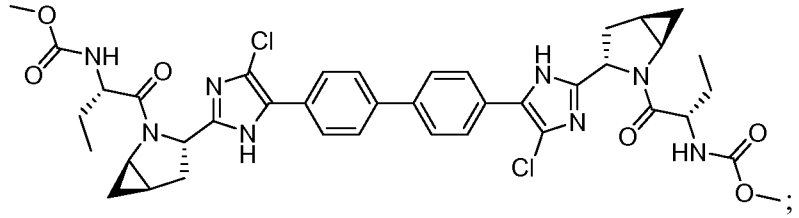
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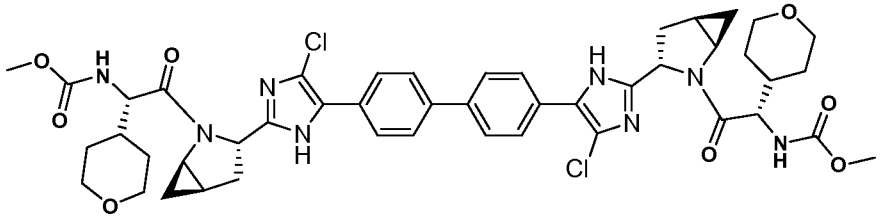


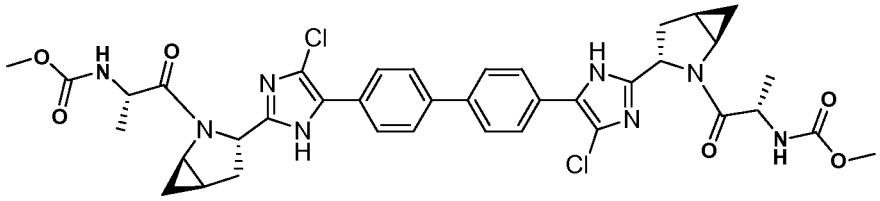
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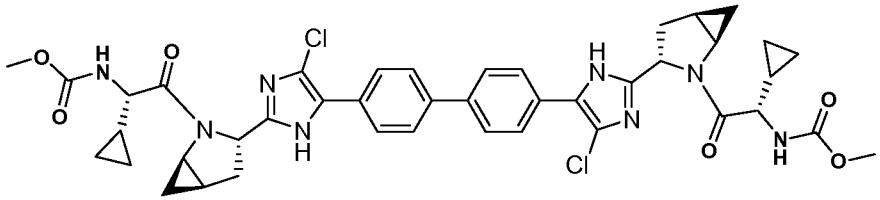


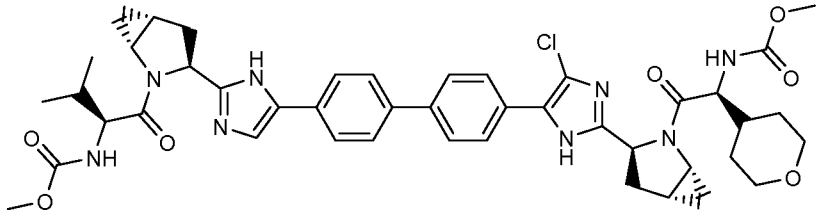
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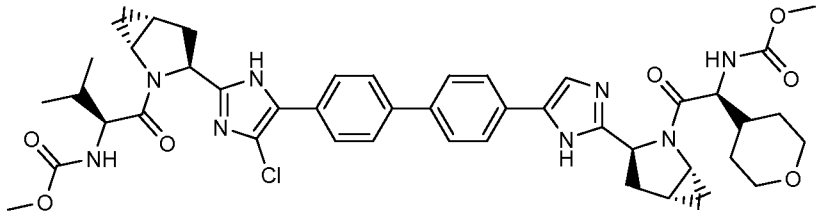

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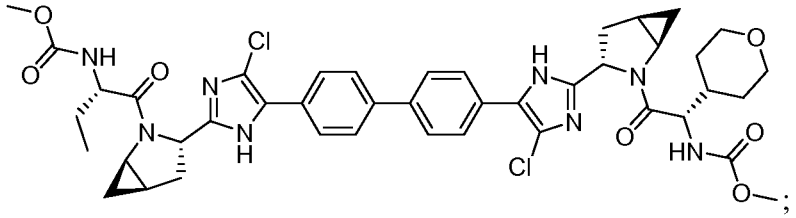

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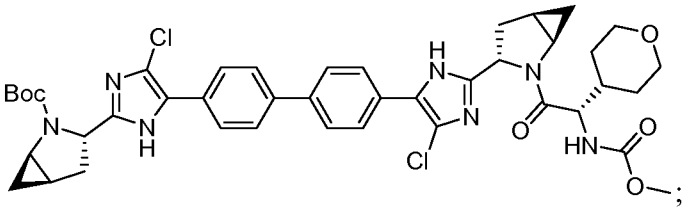

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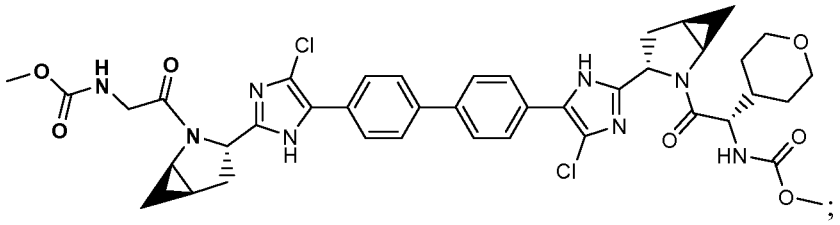

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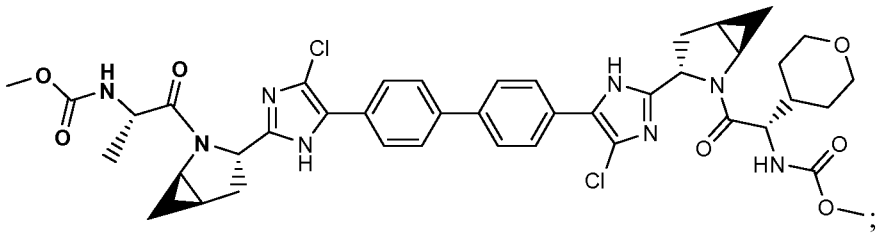

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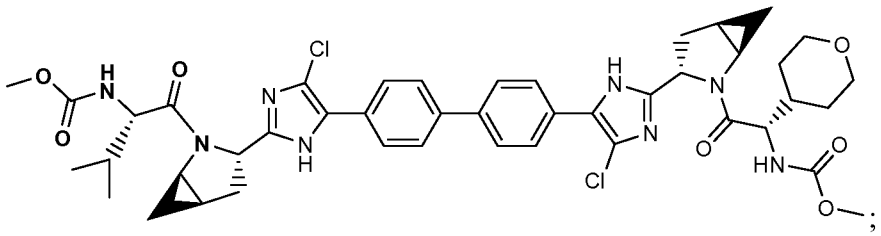

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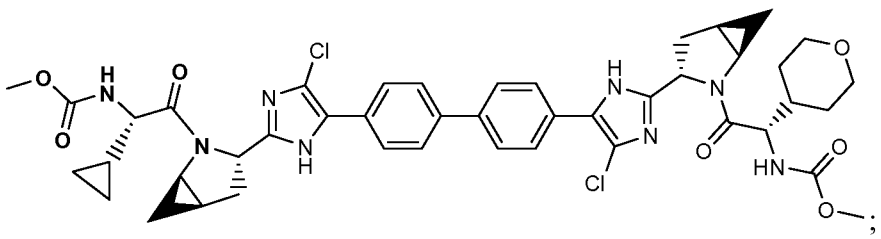


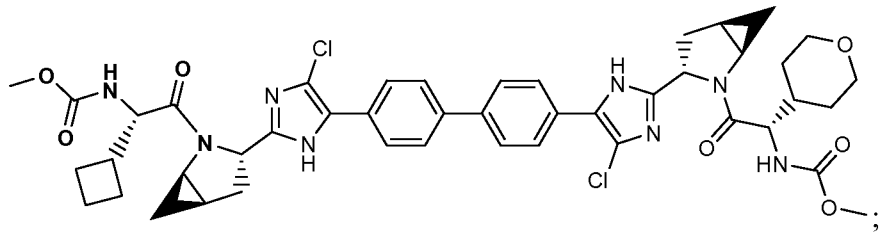


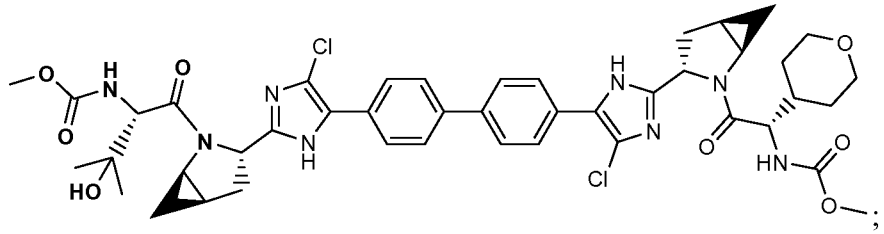


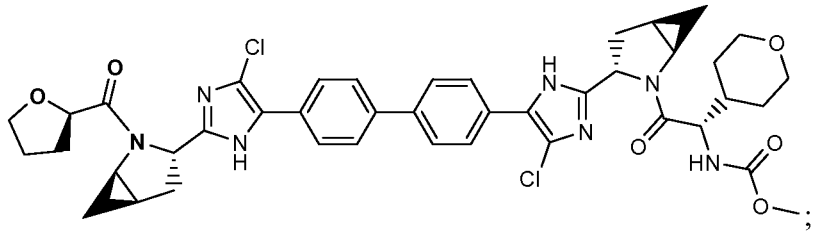


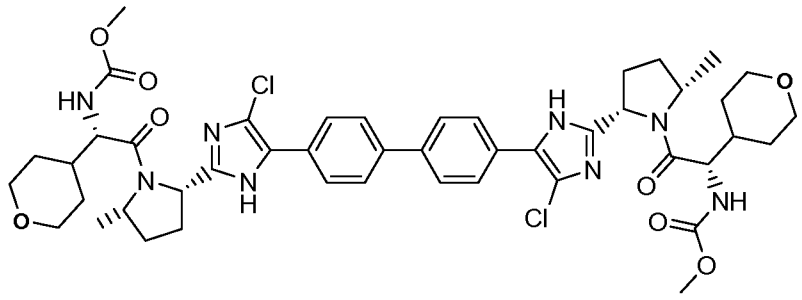




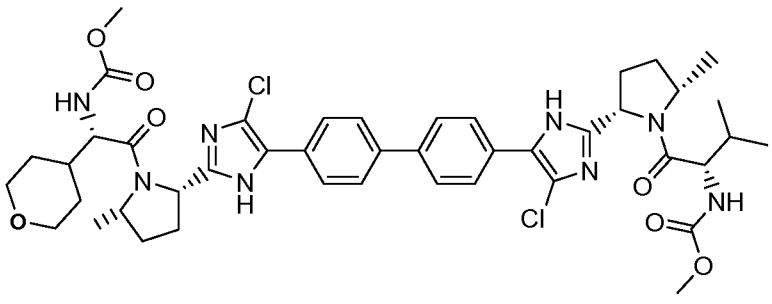




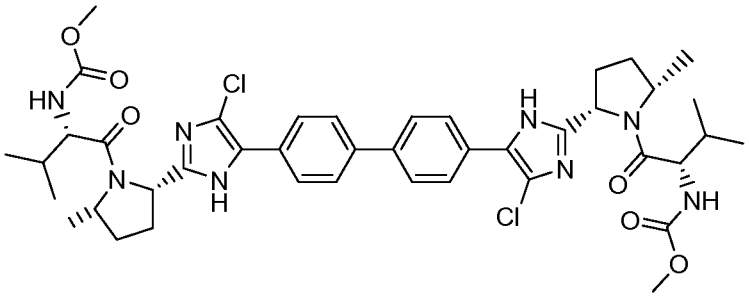


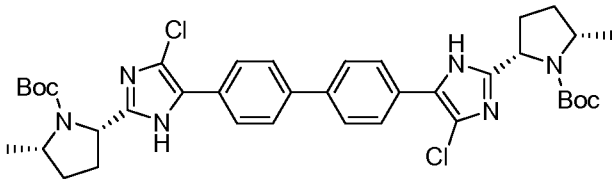


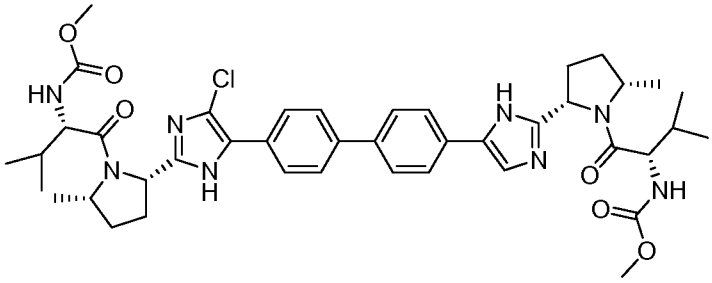
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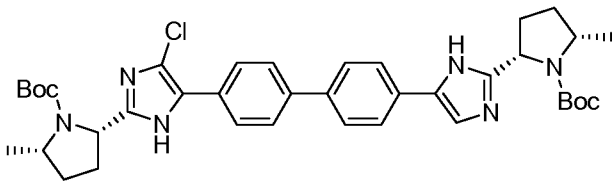


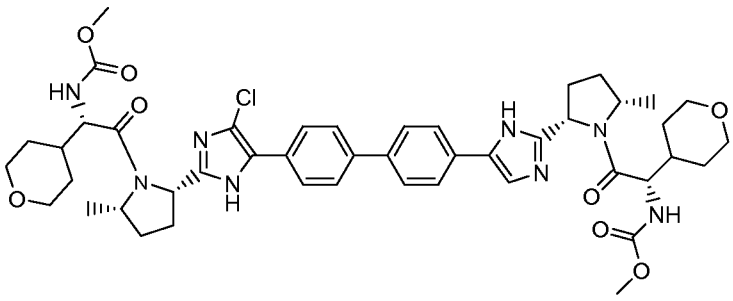
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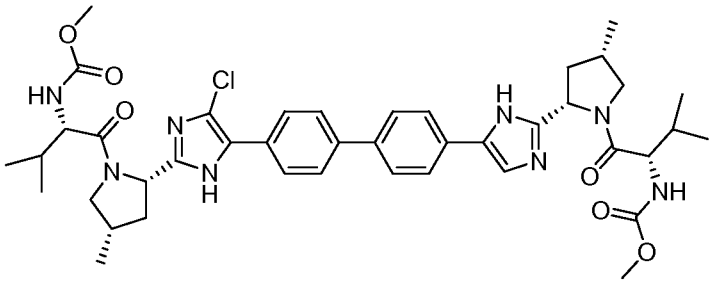

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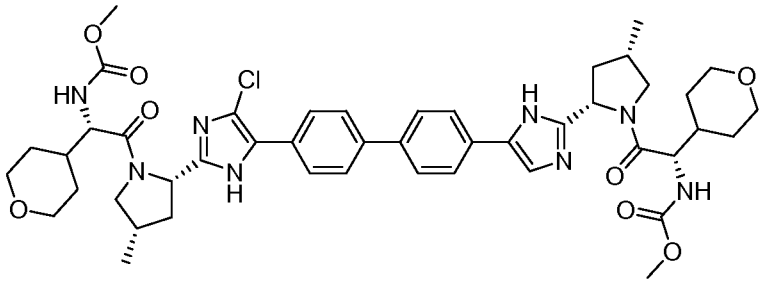

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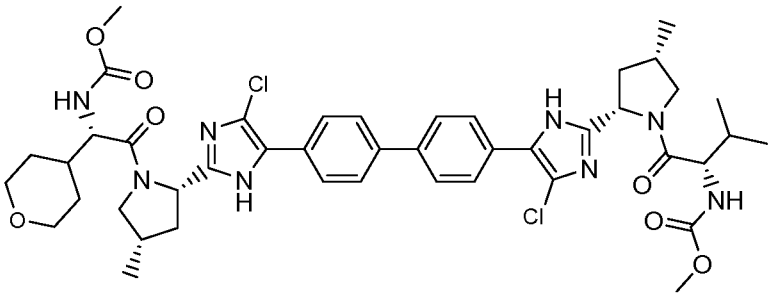

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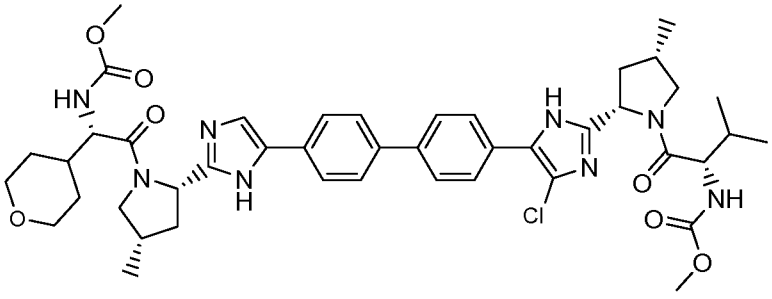

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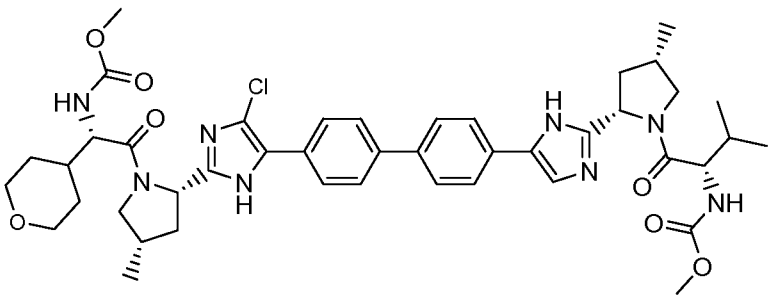

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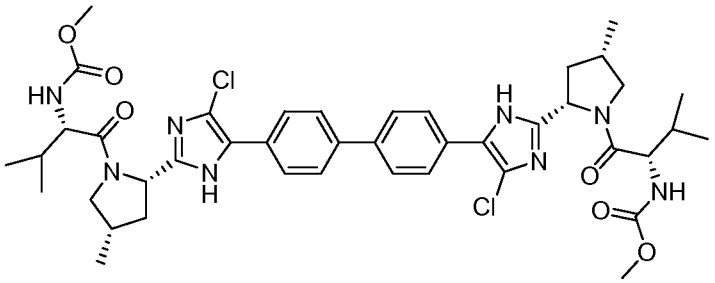

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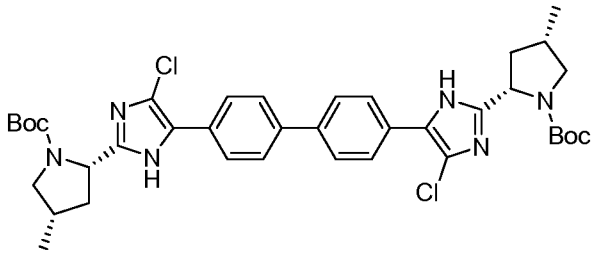

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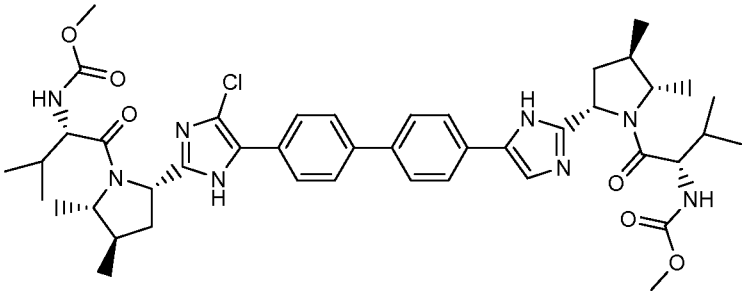

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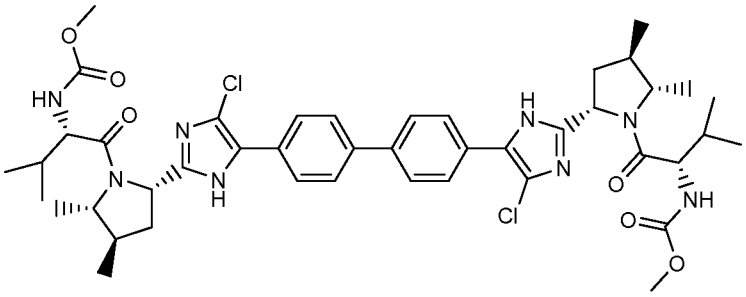

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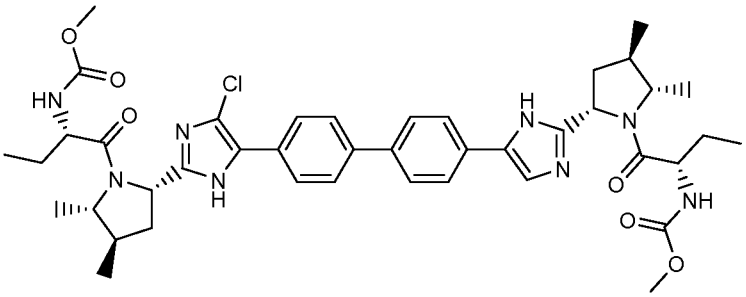

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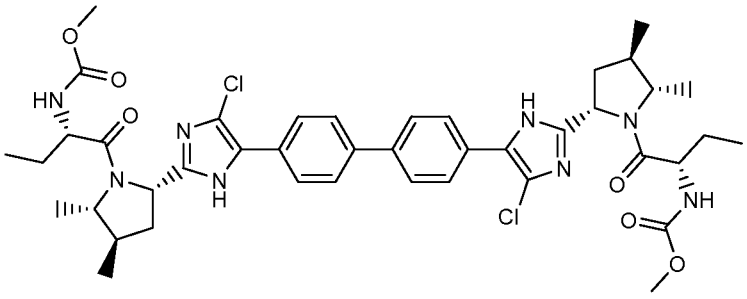

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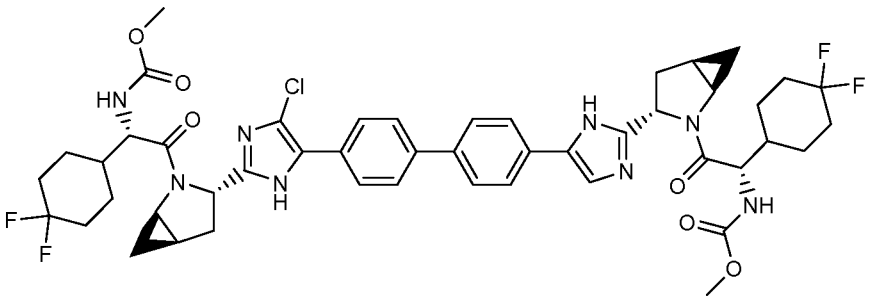

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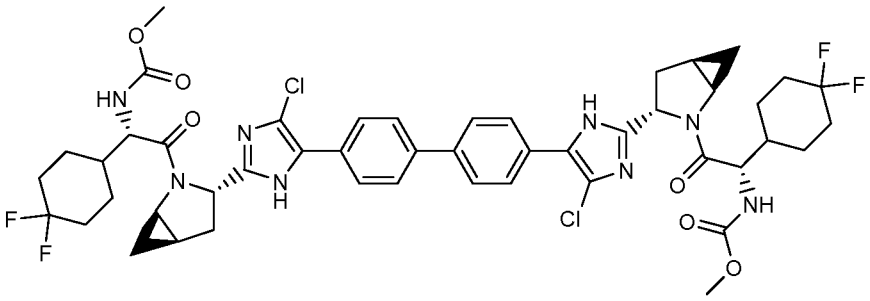

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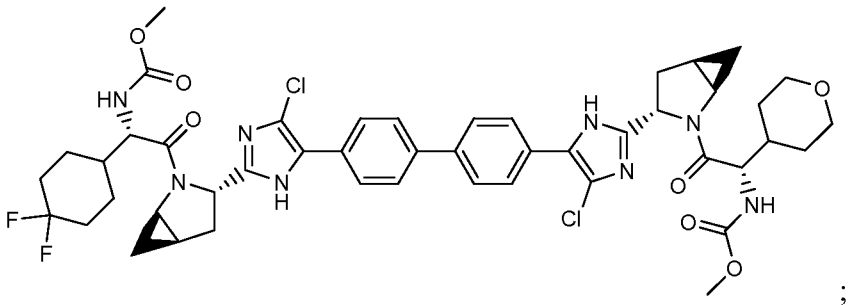

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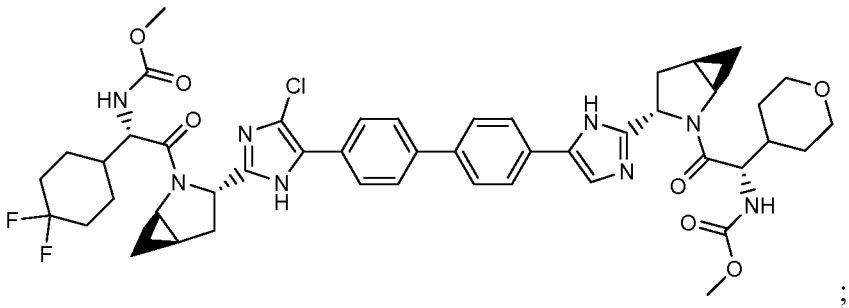

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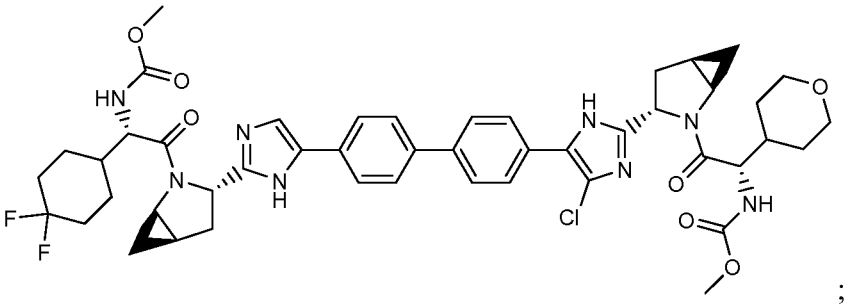

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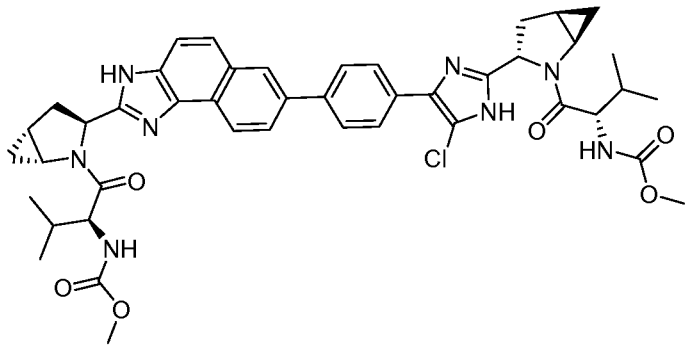

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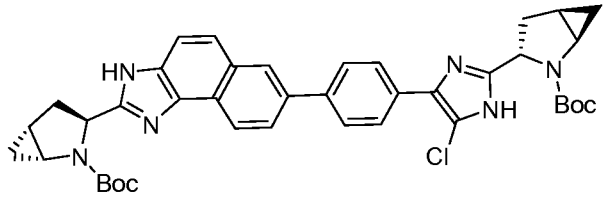

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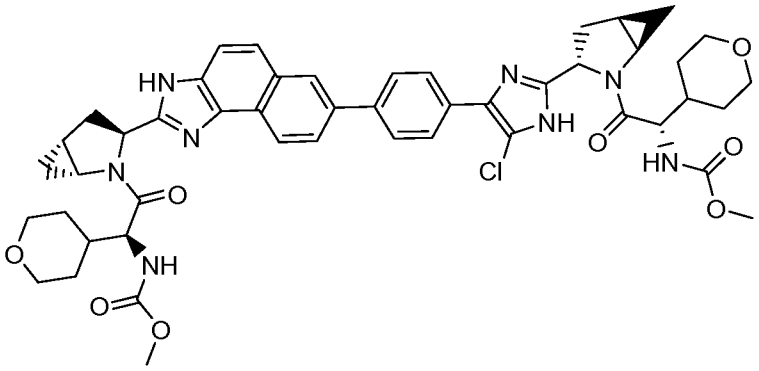

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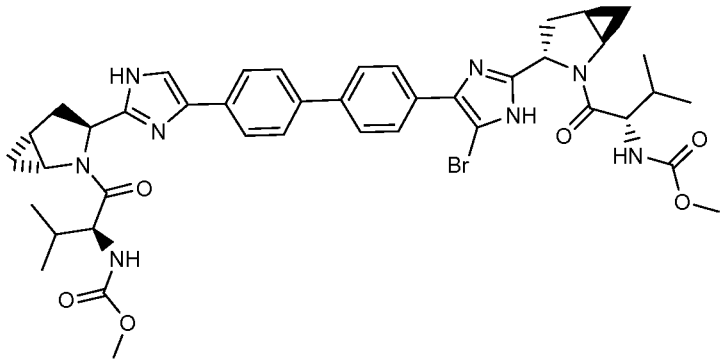

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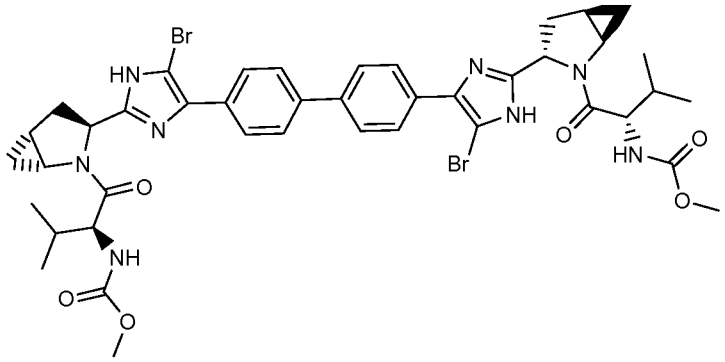

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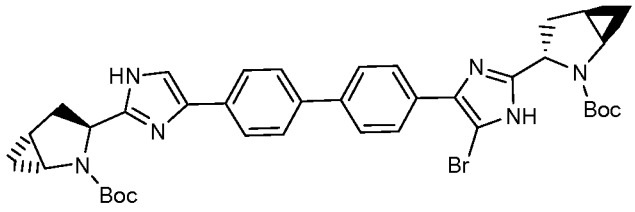

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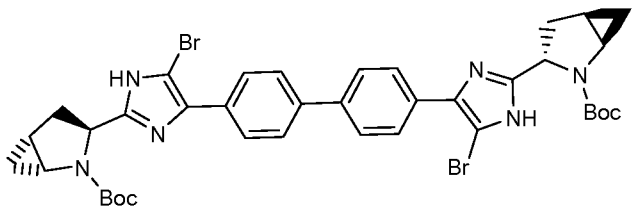
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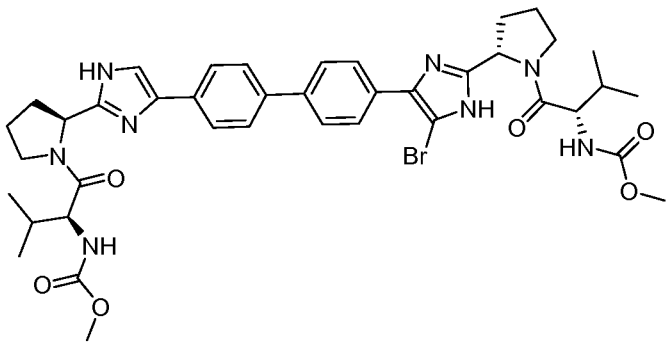
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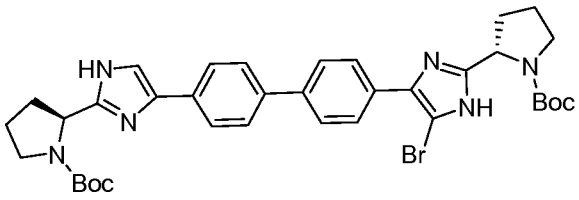
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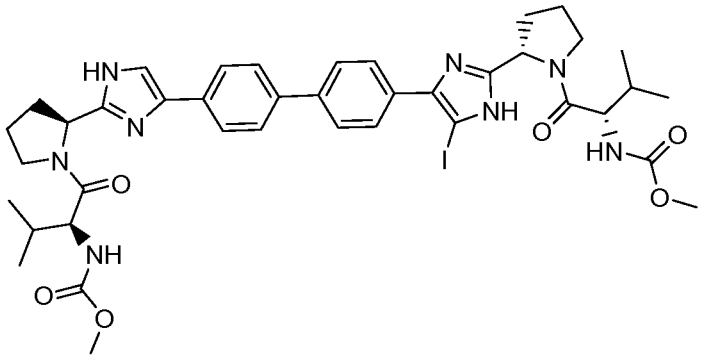
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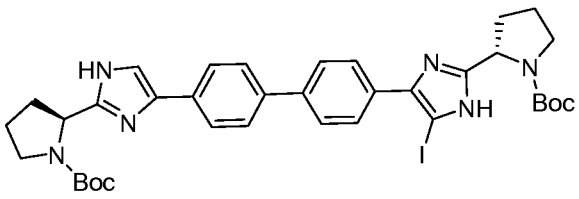
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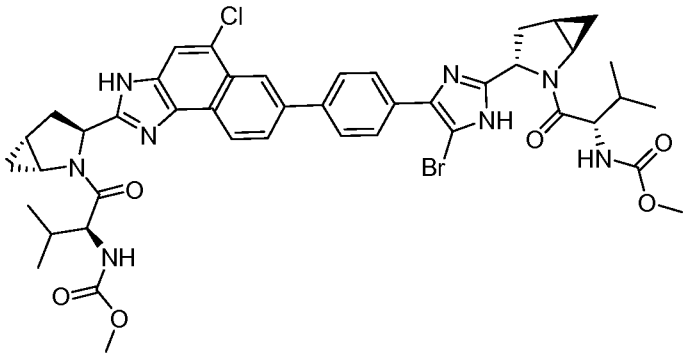
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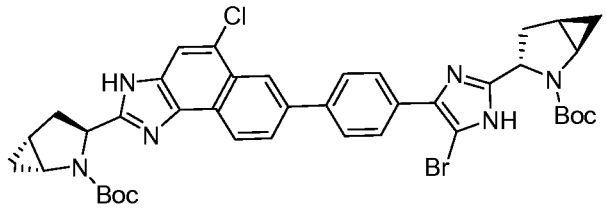
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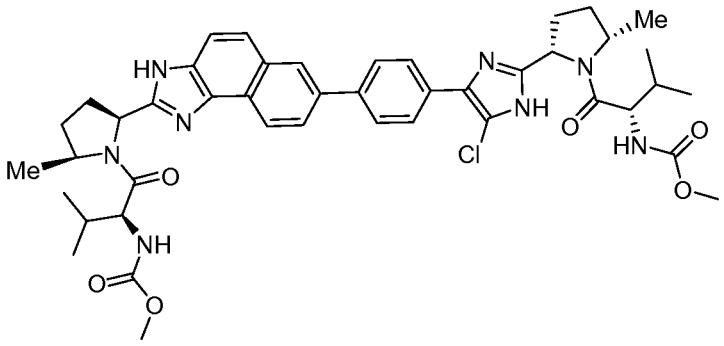
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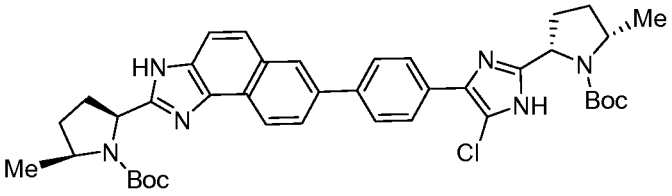
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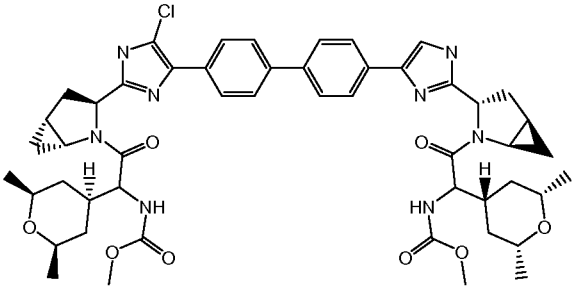
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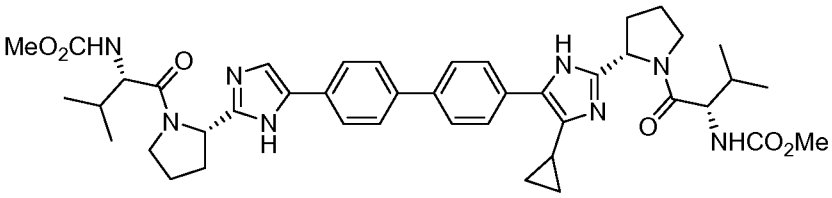
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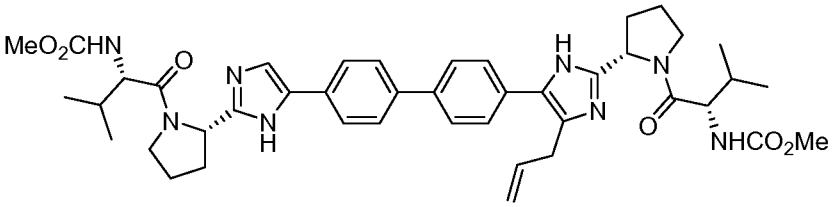
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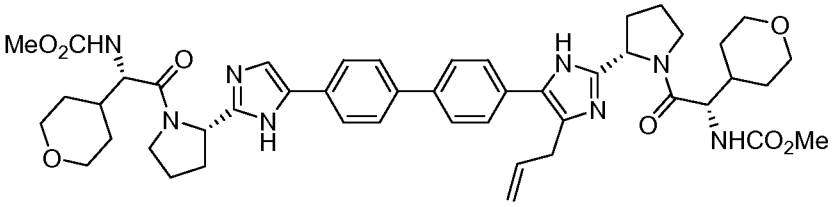
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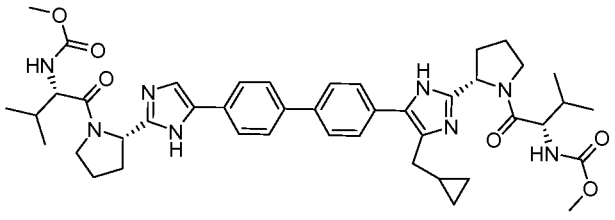
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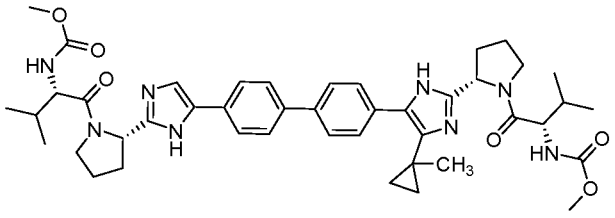

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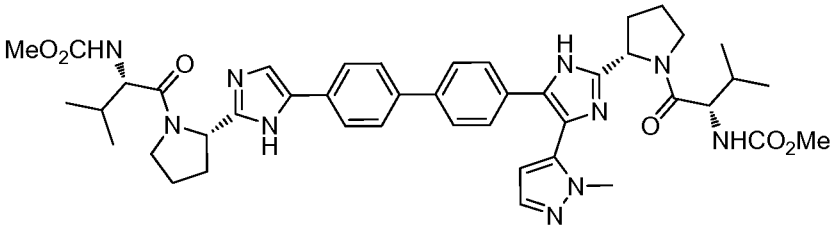
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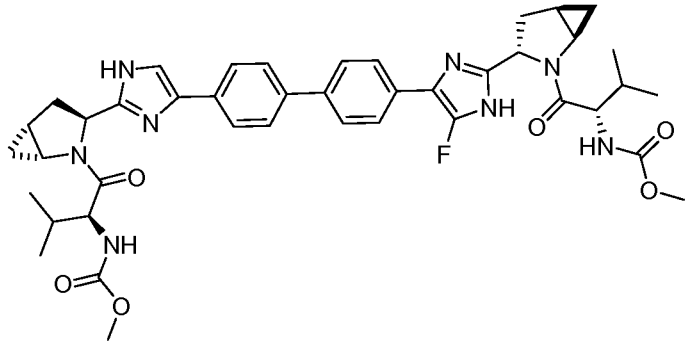

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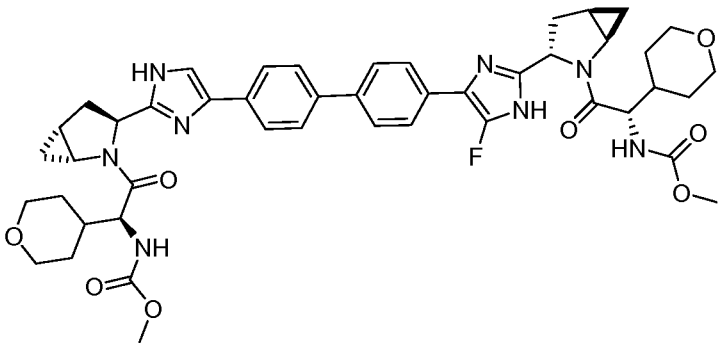
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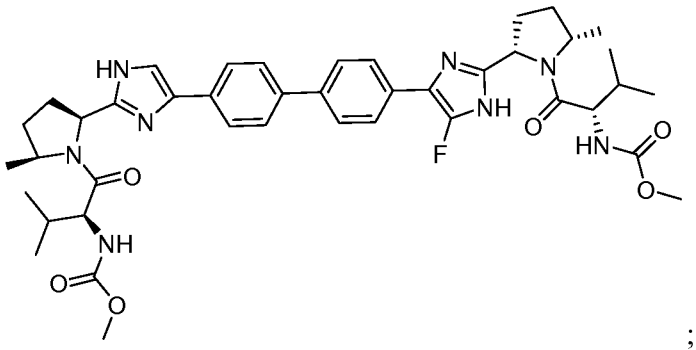

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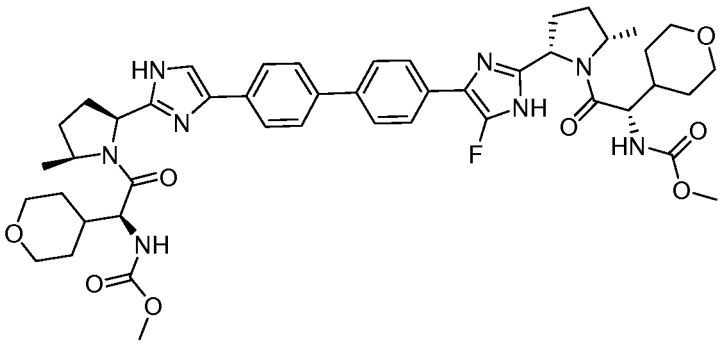

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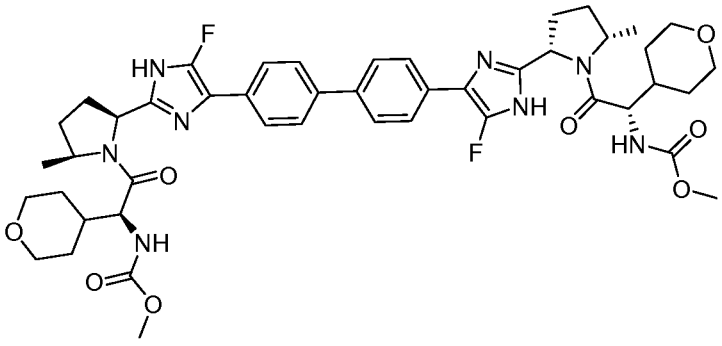

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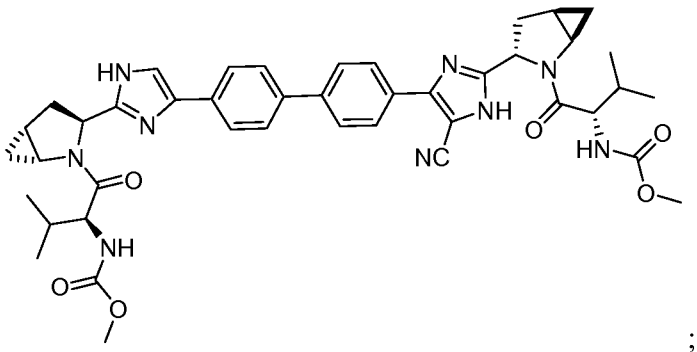
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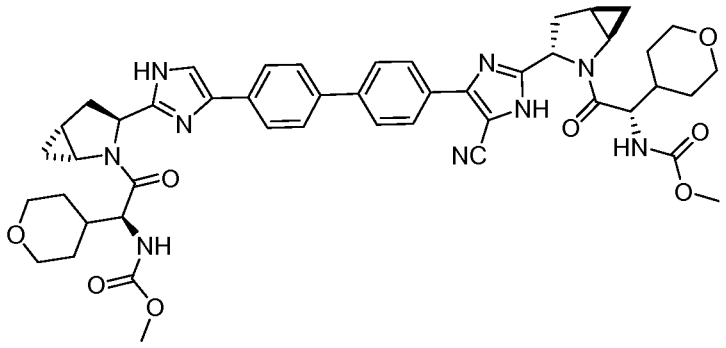
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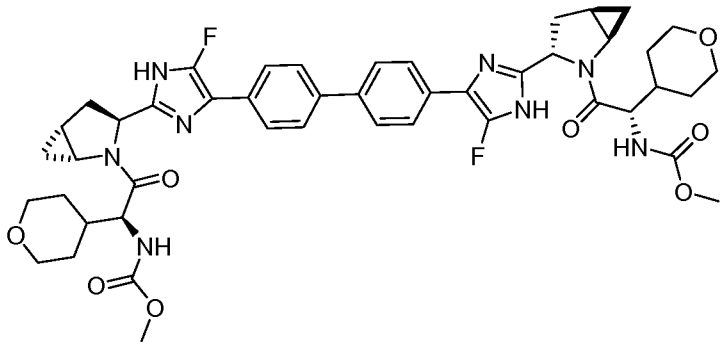
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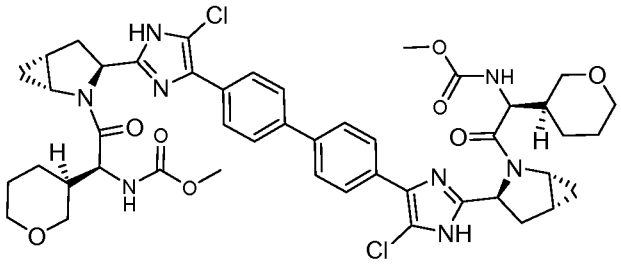
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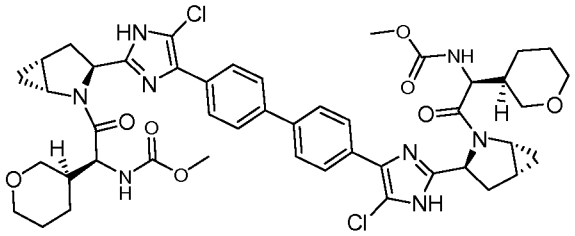
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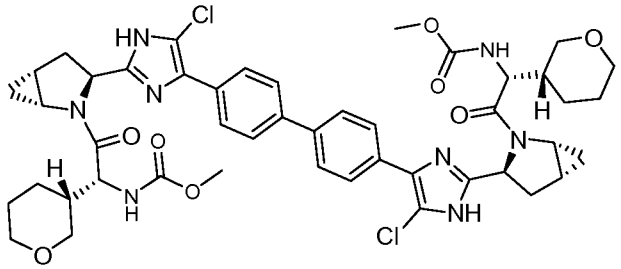
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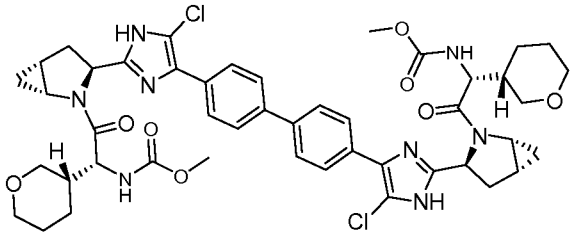
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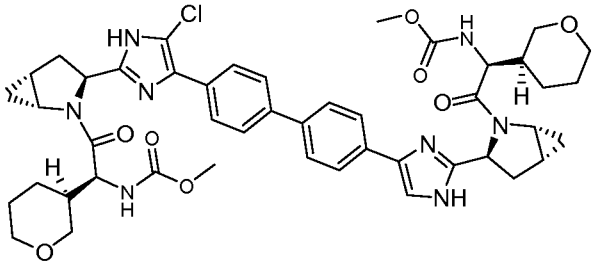


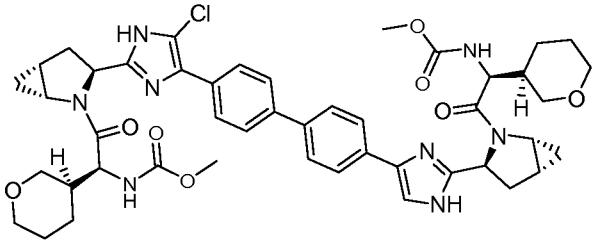
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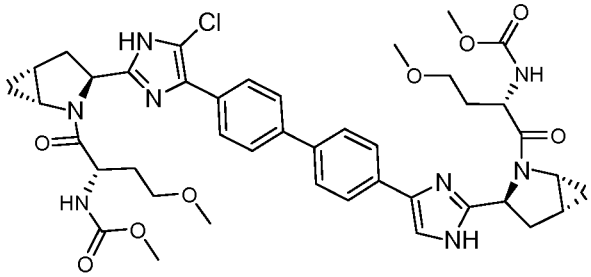


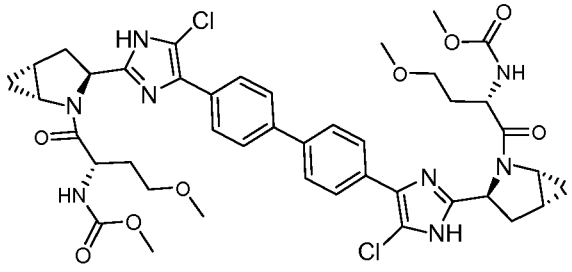
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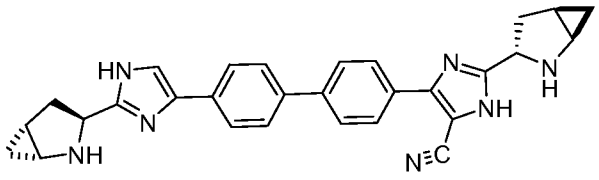

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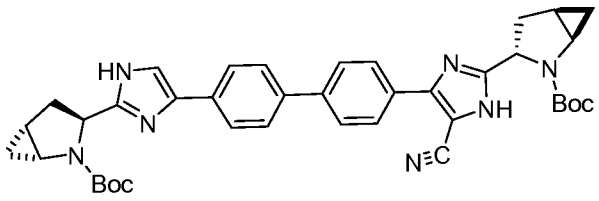

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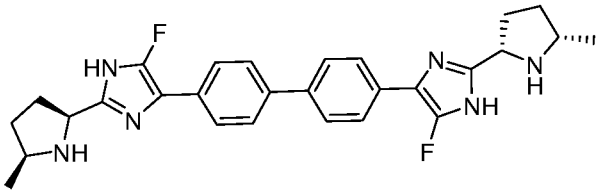

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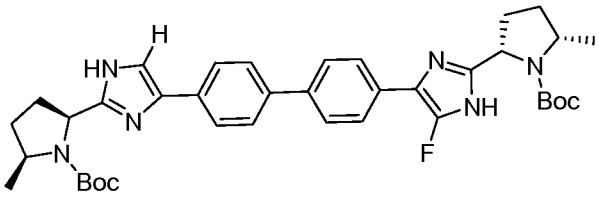

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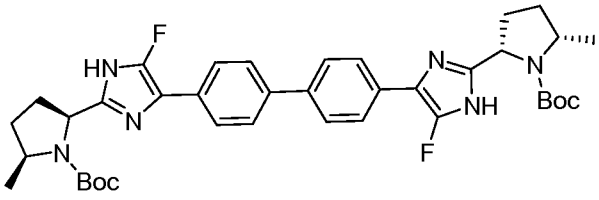

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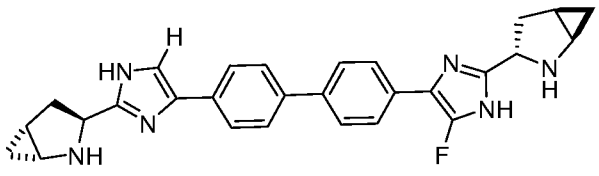

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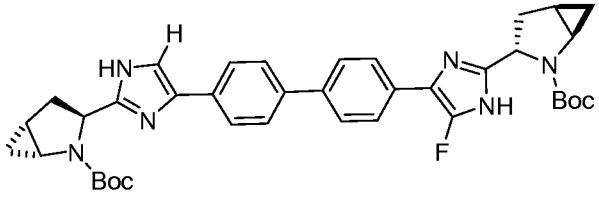

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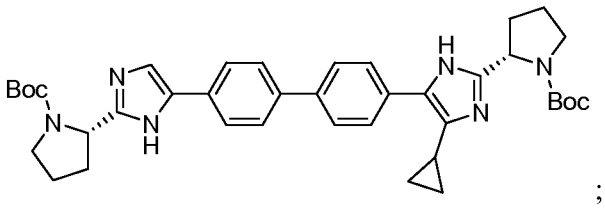

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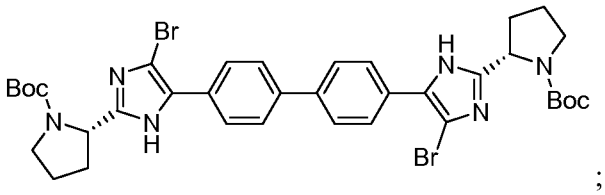

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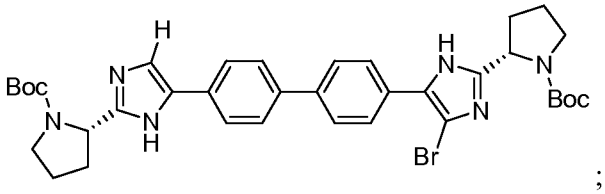

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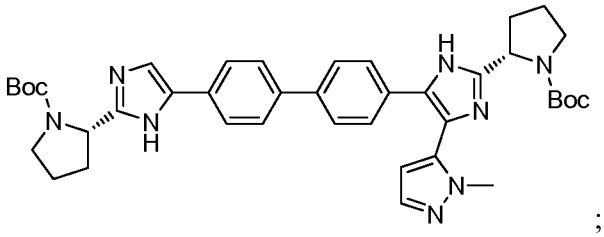

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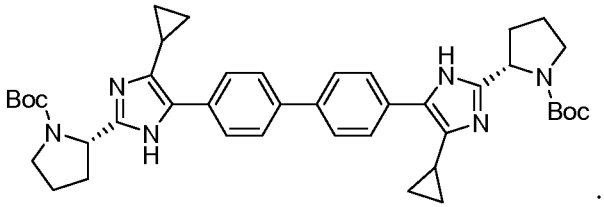
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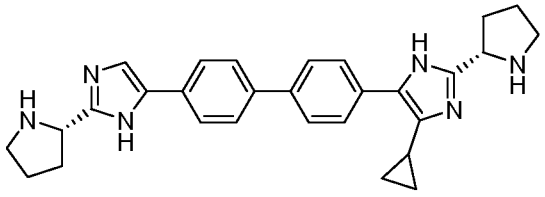

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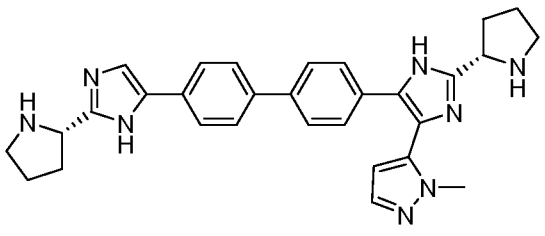

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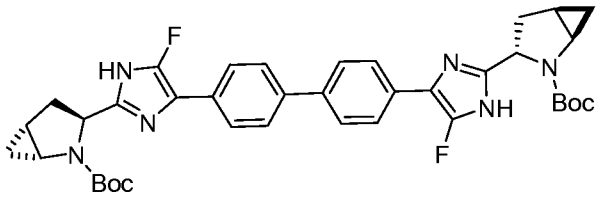

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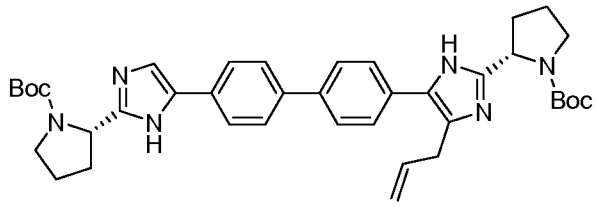

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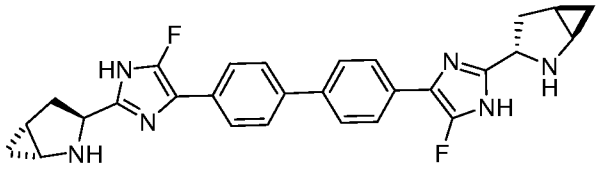

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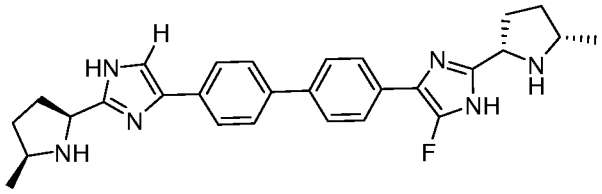
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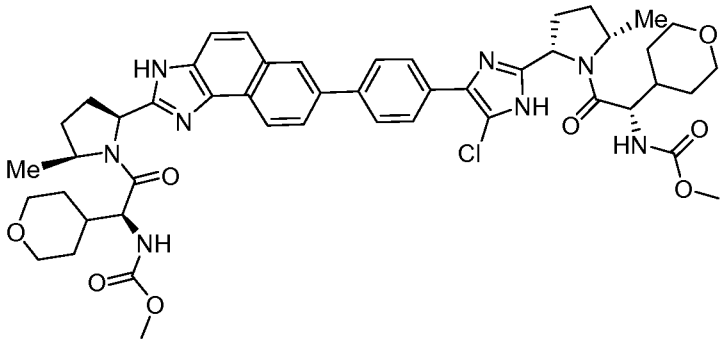
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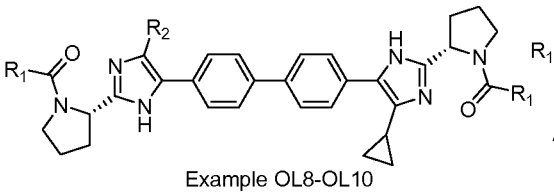
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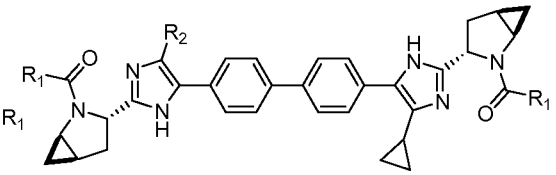
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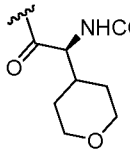
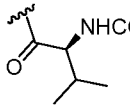
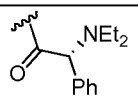
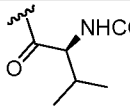
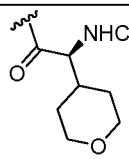
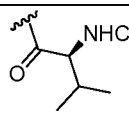
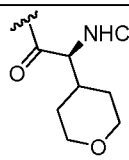
8. A compound selected from



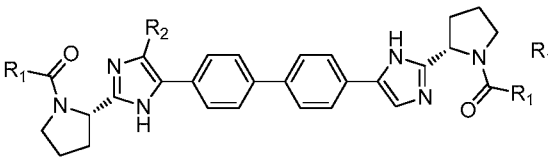
Example OL8-OL10



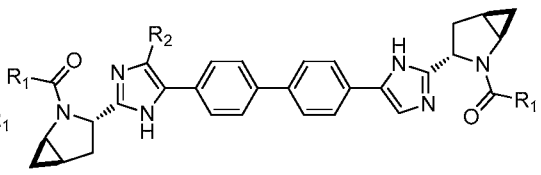
Example OL11-OL14

Example		R_2
OL8		H
OL9		
OL10		
OL11		H
OL12		H
OL13		
OL14		

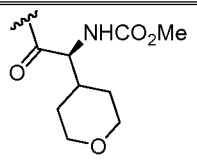
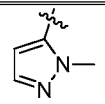
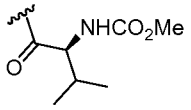
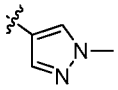
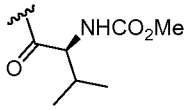
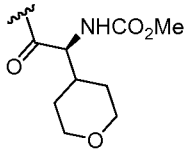
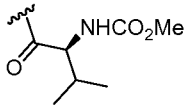
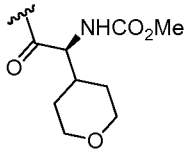
;



Example OL20-OL23



Example OL24-OL25

Example		R_2
OL20		
OL21		
OL22		
OL23		
OL24		 ; and
OL25		

;

or a pharmaceutically acceptable salt thereof.

9. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The composition of claim 9 further comprising at least one additional compound having anti-HCV activity.

11. The composition of claim 10 wherein at least one of the additional compounds is an interferon or a ribavirin.

12. The composition of claim 11 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

13. The composition of claim 10 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

14. The composition of claim 10 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

15. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15 further comprising administering at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

17. The method of claim 16 wherein at least one of the additional compounds is an interferon or a ribavirin.

18. The method of claim 17 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

19. The method of claim 16 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

20. The method of claim 16 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/060077

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 C07D405/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/062821 A1 (GLAXOSMITHKLINE LLC [US]; SCHMITZ FRANK ULRICH [US]; RAI ROOPA [US]; R) 3 June 2010 (2010-06-03) claim 1	1-20
X,P	WO 2010/111673 A1 (PRESIDIO PHARMACEUTICALS INC [US]; ZHONG MIN [US]; LI LEPING [US]) 30 September 2010 (2010-09-30) claim 1	1-20
A	WO 2009/102325 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 20 August 2009 (2009-08-20) claims 1, 3, 15 page 2, lines 21-29 page 3, lines 1-20 pages 512-537; examples J.1-J51	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2011	07/02/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guazzelli, Giuditta

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/060077

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/202478 A1 (BACHAND CAROL [CA] ET AL) 13 August 2009 (2009-08-13) claims 1, 9-11, 17	1-20

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/060077

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010062821 A1	03-06-2010	NONE	
WO 2010111673 A1	30-09-2010	NONE	
WO 2009102325 A1	20-08-2009	AU 2008350334 A1	20-08-2009
		CA 2715839 A1	20-08-2009
		EP 2242752 A1	27-10-2010
US 2009202478 A1	13-08-2009	AR 070366 A1	31-03-2010
		AU 2009214997 A1	20-08-2009
		CA 2715559 A1	20-08-2009
		EP 2245027 A1	03-11-2010
		KR 20100124290 A	26-11-2010
		PE 13812009 A1	18-09-2009
		WO 2009102633 A1	20-08-2009

INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Descripción de la Invención

La presente descripción se refiere de forma general a compuestos antivirales, y más específicamente, se refiere a compuestos que pueden inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC), a composiciones que comprenden los compuestos y a métodos para inhibir la función de la proteína NS5A.

El VHC es un importante patógeno humano que infecta a unos 170 millones de personas en todo el mundo (aproximadamente cinco veces el número de infectados por el virus de la inmunodeficiencia humana tipo 1). Una fracción sustancial de estos individuos infectados por el VHC desarrolla una enfermedad hepática progresiva grave, incluyendo cirrosis y carcinoma hepatocelular.

El actual tratamiento de referencia para el VHC, que usa una combinación de interferón pegilado y ribavirina, presenta una tasa de éxito subóptima para conseguir una respuesta vírica mantenida y provoca numerosos efectos secundarios. Por lo tanto, existe una clara y percibida necesidad desde hace mucho tiempo de desarrollar terapias eficaces para cubrir esta necesidad médica no satisfecha.

El VHC es un virus de ARN de polaridad positiva. Basándose en una comparación de la secuencia de aminoácidos

deducida y la gran similitud en la región 5’ no traducida, el VHC ha sido clasificado como un género diferente de la familia Flaviviridae. Todos los miembros de la familia Flaviviridae presentan viriones encapsulados que contienen un genoma de ARN de polaridad positiva que codifica todas las proteínas específicas del virus conocidas mediante traducción de un marco de lectura abierto, ininterrumpido y único.

Se encuentra una heterogeneidad considerable en la secuencia de nucleótidos y de aminoácidos codificados en todo el genoma del VHC debido a la alta tasa de errores de la ARN polimerasa dependiente de ARN codificado que carece de capacidad correctora. Se han caracterizado al menos seis genotipos principales y se han descrito más de 50 subtipos distribuidos por todo el mundo. La significación clínica de la heterogeneidad genética del VHC ha demostrado una propensión a la aparición de mutaciones durante el tratamiento con monoterapia, por lo tanto es deseable el uso de otras opciones de tratamiento. El posible efecto modulador de los genotipos sobre la patogénesis y la terapia sigue sin comprenderse.

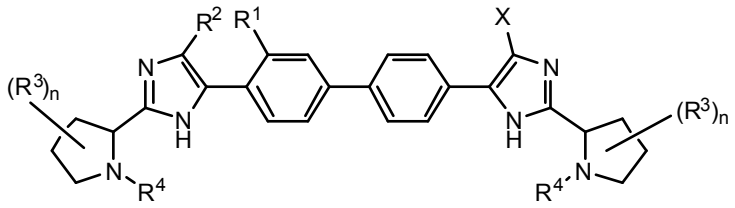
El genoma de ARN monocatenario del VHC tiene una longitud de aproximadamente 9500 nucleótidos y tiene un único marco de lectura abierto (ORF, por sus siglas en inglés) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En las células infectadas, esta

poliproteína es escindida en múltiples sitios por proteasas celulares y víricas para producir las proteínas estructurales y no estructurales (NS, por sus siglas en inglés). En el caso del VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) es llevada a cabo por dos proteasas víricas. Se cree que la primera es una metaloproteasa y escinde la unión entre NS2 y NS3; la segunda es una serina proteasa contenida en la región del extremo N de NS3 (también denominada en el presente documento proteasa NS3) y actúa de mediadora de todas las posteriores escisiones cadena abajo de NS3, tanto en cis, en el sitio de escisión de NS3 y NS4A, como en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece desempeñar varias funciones, ya sea actuando de cofactor para la proteasa NS3 como ayudando en la localización en la membrana de NS3 y otros componentes de las replicasas víricas. Para la adecuada actividad de proteasa es necesaria la formación de un complejo NS3-NS4A, lo que supone una eficacia proteolítica mayor de los eventos de escisión. La proteína NS3 también muestra actividades de nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada VHC polimerasa) es una ARN polimerasa dependiente de ARN que está implicada en la replicación del VHC con otras proteínas del VHC, entre otras NS5A, en un complejo de replicasa.

Se desean compuestos útiles para tratar pacientes

infectados por VHC que inhiban de forma selectiva la replicación viral del VHC. En particular, son deseables compuestos que sean eficaces para inhibir la función de la proteína NS5A. La proteína NS5A del VHC se describe, por ejemplo, en las siguientes referencias: S. L. Tan, et al., *Virology*, 284:1-12 (2001); K.-J. Park, et al., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, et al., *Nature*, **435**, 374 (2005); R. A. Love, et al., *J. Virol*, **83**, 4395 (2009); N. Appel, et al., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, et al., documento WO2006/093867.

En un aspecto, la presente descripción proporciona un compuesto de fórmula (I)



(I),

o una sal farmacéuticamente aceptable del mismo; en la que

n es 0, 1 ó 2;

X está seleccionado de entre hidrógeno, alquenilo, ciano, cicloalquilo, (cicloalquil)alquilo, halo y heterociclilo;

R^1 está seleccionado de entre hidrógeno y halo;

R^2 está seleccionado de entre hidrógeno, alquenilo, ciano, cicloalquilo, (cicloalquil)alquilo, halo y

heterociclilo; o

R^1 y R^2, junto con los átomos de carbono a los que están unidos, forman un anillo aromático de seis miembros sustituidos opcionalmente con un grupo halo;

con la condición de que al menos uno de X y R^2 está seleccionado de entre alquenilo, ciano, cicloalquilo, (cicloalquilalquilo), halo y heterociclilo;

cada R^3 es alquilo, en el que el alquilo puede, opcionalmente, formar un anillo condensado de tres o cuatro miembros con un átomo de carbono adyacente o un anillo espirocíclico de tres o cuatro miembros con el átomo de carbono al que está unido; en el que los anillos condensados y espirocíclicos están opcionalmente sustituidos con uno o dos grupos alquilo;

cada R^4 está seleccionado independientemente de hidrógeno y $-C(O)R^5$; y

cada R^5 está seleccionado independientemente de alcoxi, alquilo, arilalcoxi, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

En una primera modalidad del primer aspecto, la presente descripción proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en el que cada R^5 está seleccionado de forma independiente de alcoxi, heterociclilo y (NR^cR^d)alquilo.

En una segunda modalidad del primer aspecto, la presente descripción proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en la que X es halo. En una tercera modalidad del primer aspecto, R^2 es halo.

En una cuarta modalidad del primer aspecto, la presente descripción proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en el que R^1 y R^2, junto con los átomos de carbono a los que están unidos, forman un anillo aromático de seis miembros opcionalmente sustituido con un grupo halo.

En una quinta modalidad del primer aspecto, la presente descripción proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que X es hidrógeno.

En un segundo aspecto, la presente descripción proporciona una composición que comprende un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable. En una primera modalidad del segundo aspecto, la composición comprende además al menos un compuesto adicional que tenga actividad contra el VHC. En una segunda modalidad del segundo aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del segundo aspecto, el interferón está seleccionado de entre interferón alfa-2B, interferón alfa pegilado, interferón consenso,

interferón alfa-2A e interferón linfoblastoide tau.

En una cuarta modalidad del segundo aspecto, la presente descripción proporciona una composición que comprende un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable, y al menos un compuesto adicional que presenta actividad contra VHC, en la que al menos uno de los compuestos adicionales está seleccionado a partir de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T cooperadores de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad del segundo aspecto, la presente descripción proporciona una composición que comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable y al menos un compuesto adicional que tenga actividad contra el VHC, en la que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC e IMPDH para el

tratamiento de una infección por VHC.

En un tercer aspecto, la presente descripción proporciona un método de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo. En una primera modalidad del tercer aspecto, el método comprende además administrar al menos un compuesto adicional que tenga actividad contra el VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una segunda modalidad del tercer aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del tercer aspecto, el interferón está seleccionado de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

En una cuarta modalidad del tercer aspecto, la presente descripción proporciona un método para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y al menos un compuesto adicional que tenga actividad contra VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en el que al menos uno de los compuestos

adicionales está seleccionado de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T auxiliares de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad del tercer aspecto, la presente descripción proporciona un método para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y al menos un compuesto adicional que tenga actividad contra VHC antes, después o simultáneamente al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana que está seleccionado a partir de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC e IMPDH para el tratamiento de una infección por VHC.

Otros aspectos de la presente modalidad pueden incluir combinaciones adecuadas de modalidades descritas en el presente documento.

Se pueden encontrar aún otros aspectos y

modalidades en la descripción proporcionada en el presente documento.

La descripción de la presente descripción en el presente documento se interpretaría de forma congruente con las leyes y principios de la formación de enlaces químicos. En algunos casos, puede ser necesario eliminar un átomo de hidrógeno para acomodar un sustituyente en cualquier lugar dado.

Se entenderá que los compuestos comprendidos por la presente descripción son aquellos que son adecuadamente estables para usar como un agente farmacéutico.

Se debe interpretar que la definición de cualquier sustituyente o variable en una localización particular en una molécula sea independiente de sus definiciones en otro lugar en esa molécula. Por ejemplo, cuando R^1 y R^2 contienen ambos un grupo R^4, los dos grupos R^4 pueden ser iguales o diferentes.

Todas las patentes, solicitudes de patentes y referencias bibliográficas citadas en la invención se incorporan en el presente documento por referencia en su totalidad. En el caso de contradicciones, la presente descripción, incluyendo definiciones, prevalecerá.

Tal como se usa en el presente documento descriptivo, los siguientes términos tienen los significados indicados:

Como se usa en el presente documento, las formas del singular “un”, “uno” y “el/la” incluyen referencia al plural a menos que el contexto indique claramente lo contrario.

A no ser que se indique de otro modo, todos los grupos arilo, cicloalquilo y heterociclilo de la presente descripción pueden estar sustituidos como se describe en cada una de sus respectivas definiciones. Por ejemplo, la parte arilo de un grupo arilalquilo puede estar sustituida como se describe en la definición del término “arilo”.

El término “alquenilo”, como se usa en el presente documento, se refiere a un grupo de cadena lineal o ramificada de dos a seis átomos de carbono que contiene al menos un doble enlace carbono-carbono.

El término “alqueniloxi”, tal como se usa en el presente documento, se refiere a un grupo alquenilo unido a un resto molecular principal mediante un átomo de oxígeno.

El término “alqueniloxicarbonilo,” tal como se usa en el presente documento, se refiere a un grupo alqueniloxi unido a un resto molecular principal mediante un grupo carbonilo.

El término “alcoxi”, como se usa en el presente documento, se refiere a un grupo alquilo unido al resto molecular principal a través de un átomo de oxígeno.

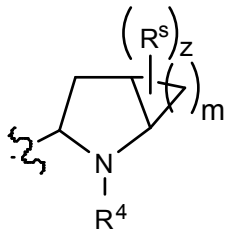
El término “alcoxialquilo,” tal como se usa en el

presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alcoxi.

El término "alcoxialquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxialquilo unido al grupo molecular principal a través de un grupo carbonilo.

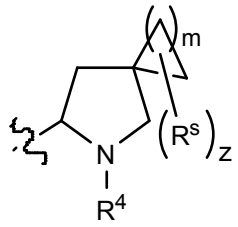
El término "alcoxicarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxi unido al grupo molecular principal a través de un grupo carbonilo.

El término "alquilo," tal como se usa en el presente documento, se refiere a un grupo derivado de un grupo hidrocarburo saturado de cadena lineal o ramificada que contiene de uno a seis átomos de carbono. En los compuestos de la presente descripción, cuando R^3 es alquilo, el alquilo puede formar, opcionalmente, un anillo de tres o cuatro miembros condensado con un átomo de carbono adyacente para proporcionar la estructura mostrada a continuación:



en la que m está seleccionado de entre 1 y 2, en la que z es 0, 1, ó 2, y en la que R^s es alquilo; o en la que el alquilo puede formar, opcionalmente, un anillo espirocíclico de tres o cuatro miembros con el átomo de carbono al que está unido,

para proporcionar la estructura mostrada a continuación:



en la que m está seleccionado entre 1 y 2; en la que z es 0, 1 ó 2, y en la que R^s es alquilo.

El término "alquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alquilo unido al resto molecular principal a través de un grupo carbonilo.

El término "alquilcarboniloxi", tal como se usa en el presente documento, se refiere a un grupo alquilcarbonilo unido a un resto molecular principal mediante un átomo de oxígeno.

El término "alquilsulfanilo", tal como se usa en el presente documento, se refiere a un grupo alquilo unido a un resto molecular principal mediante un átomo de azufre.

El término "alquilsulfonilo," tal como se usa en el presente documento, se refiere a un grupo alquilo unido a un resto molecular principal mediante un grupo sulfonilo.

El término "arilo," tal como se usa en el presente documento, se refiere a un grupo fenilo o un sistema de anillo bicíclico condensado en el que uno o ambos de los anillos es un grupo fenilo. Los sistemas de anillo bicíclico condensado están constituidos por un grupo fenilo condensado

con un anillo carbocíclico aromático o no aromático de cuatro a seis miembros. Los grupos arilo de la presente descripción pueden estar unidos al resto molecular principal a través de cualquier átomo de carbono sustituible en el grupo. Ejemplos representativos de grupos arilo incluyen, aunque sin quedar limitados a los mismos, indanilo, indenilo, naftilo, fenilo y tetrahidronaftilo. Los grupos arilo de la presente descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alquenilo, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, un segundo grupo arilo, arilalcoxi, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo, oxo y $-P(O)OR_2$, donde cada R está seleccionado independientemente de hidrógeno y alquilo; y donde la parte alquilo del arilalquilo y el heterociclilalquilo está no sustituida y donde el segundo grupo arilo, la parte arilo del arilalquilo, la parte arilo del arilcarbonilo, el heterociclilo y la parte heterociclilo del heterociclilalquilo y el heterociclilcarbonilo están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término “arilalcoxi”, tal como se usa en el

presente documento, se refiere a un grupo arilo unido al resto molecular principal a través de un grupo alcoxi.

El término "arilalcoxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo arilalcoxi unido a un resto molecular principal a través de un grupo carbonilo.

El término "arilalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos arilo. La parte alquilo del arilalquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi y $-NR^cR^d$, estando el heterociclilo además opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo, haloalcoxi, haloalquilo, hidroxi, $-NR^xR^y$ y oxo.

El término "arilalquilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo arilalquilo unido a un resto molecular principal mediante un grupo carbonilo.

El término "arilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo arilo unido a un resto molecular principal mediante un grupo carbonilo.

El término “ariloxi”, como se usa en el presente documento, se refiere a un grupo arilo unido al resto molecular principal a través de un átomo de oxígeno.

El término “ariloxicarbonilo,” tal como se usa en el presente documento, se refiere a un grupo ariloxi unido a un resto molecular principal a través de un grupo carbonilo.

El término “arilsulfonilo,” tal como se usa en el presente documento, se refiere a un grupo arilo unido a un resto molecular principal mediante un grupo sulfonilo.

El término “carbonilo”, como se usa en el presente documento, se refiere a -C(O)-.

El término “carboxi,” tal como se usa en el presente documento, se refiere a $-CO_2H$.

El término “ciano”, tal como se usa en el presente documento, se refiere a -CN.

El término “cicloalquilo,” tal como se usa en la presente invención, se refiere a un sistema de anillo hidrocarbonado saturado monocíclico que tiene de tres a siete átomos y ningún heteroátomo. Ejemplos representativos de grupos cicloalquilo incluyen, pero no están limitados a, ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo de la presente descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo, ciano, halo, haloalcoxi, haloalquilo,

heterociclilo, hidroxi, hidroxialquilo, nitro y $-NR^xR^y$, estando el arilo y el heterociclilo además opcionalmente sustituidos con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, hidroxi y nitro.

El término "(cicloalquil)alquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos cicloalquilo.

El término "cicloalquiloxi", tal como se usa en el presente documento, se refiere a un grupo cicloalquilo unido al resto molecular principal a través de un átomo de oxígeno.

El término "cicloalquiloxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo cicloalquiloxi unido al resto molecular principal a través de un grupo carbonilo.

El término "cicloalquilsulfonilo", tal como se usa en el presente documento, se refiere a un grupo cicloalquilo unido al grupo molecular principal a través de un grupo sulfonilo.

El término "formilo," tal como se usa en el presente documento, se refiere a -CHO.

El término "halo", tal como se usa en el presente documento, se refieren a Cl, Br, F o I.

El término "haloalcoxi", como se usa en el presente documento, se refiere a un grupo haloalquilo unido al resto

molecular principal a través de un átomo de oxígeno.

El término "haloalcoxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo haloalcoxi unido al resto molecular principal a través de un grupo carbonilo.

El término "haloalquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, tres o cuatro átomos de halógeno.

El término "heterociclilo", tal como se usa en el presente documento, se refiere a un anillo de cuatro, cinco, seis o siete miembros que contiene uno, dos, tres o cuatro heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre. El anillo de cuatro miembros no tiene ningún doble enlace, el anillo de cinco miembros tiene de ninguno a dos dobles enlaces y los anillos de seis y siete miembros tienen de ninguno a tres dobles enlaces. El término "heterociclilo" también incluye grupos bicíclicos en los que el anillo heterociclilo está condensado con otro grupo heterociclilo monocíclico o un anillo carbocíclico aromático o no aromático de cuatro a seis miembros; así como grupos bicíclicos con puente tales como 7-azabiciclo[2.2.1]hept-7-ilo, 2-azabiciclo[2.2.2]oct-2-ilo, 2,5-diazabiciclo[2.2.1]heptan-2ilo y 2-azabiciclo[2.2.2]oct-3-ilo. Los grupos heterociclilo de la presente descripción pueden estar unidos al resto molecular principal a través de

cualquier átomo de carbono o átomo de nitrógeno en el grupo. Ejemplos de grupos heterociclilo incluyen, pero no están limitados a, benzotienilo, furilo, imidazolilo, indolinilo, indolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, quinolinilo, tetrahidropiranilo, tetrahidropiranilo, tiazolilo, tienilo y tiomorfolinilo. Los grupos heterociclilo de la presente descripción están opcionalmente sustituidos con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alquenilo, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, un segundo grupo heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxilo, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo y oxo, en los que la parte alquilo del arilalquilo y el heterociclilalquilo está no sustituida y en los que el arilo, la parte arilo del arilalquilo, la parte arilo del arilcarbonilo, el segundo grupo heterociclilo y la parte heterociclilo del heterociclilalquilo y el heterociclilcarbonilo están además opcionalmente sustituidas con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término “heterociclilalcoxi”, tal como se usa en la presente invención, se refiere a un grupo heterociclilo unido al resto molecular principal a través de un grupo alcoxi.

El término “heterociclilalcoxicarbonilo,” tal como se usa en el presente documento, se refiere a un grupo heterociclilalcoxi unido al resto molecular principal a través de un grupo carbonilo.

El término “heterociclilalquilo,” tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterociclilo. La parte alquilo del heterociclilalquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, arilo, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^cR^d$, estando el arilo además opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^xR^y$.

El término “heterociclilalquilcarbonilo,” tal como se usa en el presente documento, se refiere a un grupo heterociclilalquilo unido al resto molecular principal a través de un grupo carbonilo.

El término “heterociclilcarbonilo,” tal como se usa

en el presente documento, se refiere a un grupo heterociclilo unido al resto molecular principal a través de un grupo carbonilo.

El término "heterocicliloxi," tal como se usa en el presente documento, se refiere a un grupo heterociclilo unido a un resto molecular principal mediante un átomo de oxígeno.

El término "heterocicliloxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo heterocicliloxi unido al resto molecular principal a través de un grupo carbonilo.

El término "hidroxi", como se usa en el presente documento, se refiere a -OH.

El término "hidroxialquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos hidroxilo.

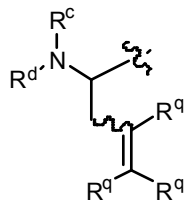
El término "hidroxialquilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo hidroxialquilo unido al resto molecular principal a través de un grupo carbonilo.

El término "nitro", tal como se usa en el presente documento, se refiere a $-NO_2$.

El término "$-NR^cR^d$," tal como se usa en el presente documento, se refiere a dos grupos, R^c y R^d, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^c y R^d están seleccionados independientemente de

hidrógeno, alqueniloxicarbonilo, alcoxialquilcarbonilo, alcoxicarbonilo, alquilo, alquilcarbonilo, cicloalquiloxi, alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, ariloxicarbonilo, arilsulfonilo, cicloalquilo, cicloalquiloxicarbonilo, cicloalquilsulfonilo, formilo, haloalcoxicarbonilo, heterociclilo, heterociclilalcoxicarbonilo, heterociclilalquilo, heterociclilalquilcarbonilo, heterociclilcarbonilo, heterocicliloxicarbonilo, hidroxialquilcarbonilo, (NR^eR^f)alquilo, (NR^eR^f)alquilcarbonilo, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, -C(NCN)OR' y $-C(NCN)NR^xR^y$, donde R' está seleccionado de alquilo y fenilo no sustituido y donde la parte alquilo del arilalquilo, el arilalquilcarbonilo, el heterociclilalquilo y el heterociclilalquilcarbonilo están además opcionalmente sustituidos con un grupo $-NR^eR^f$; y donde el arilo, la parte arilo del arilalcoxicarbonilo, el arilalquilo, el arilalquilcarbonilo, el arilcarbonilo, el ariloxicarbonilo y el arilsulfonilo, el heterociclilo y la parte heterociclilo del heterociclilalcoxicarbonilo, el heterociclilalquilo, el heterociclilalquilcarbonilo, el heterociclilcarbonilo y el heterocicliloxicarbonilo están además opcionalmente sustituidos con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "(NR^cR^d)alquenilo", tal como se usa en el presente documento, se refiere a



;

en la que R^c y R^d son como se definen en el presente documento y cada uno de R^q es independientemente hidrógeno o alquilo C_{1-3}.

El término "(NR^cR^d)alquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^cR^d$. La parte alquilo del (NR^cR^d)alquilo está además opcionalmente sustituida con uno o dos grupos adicionales seleccionados de alcoxi, alcoxialquilcarbonilo, alcoxicarbonilo, alquilsulfanilo, arilalcoxicarbonilo, carboxi, cicloalquilo, heterociclilo, heterociclilcarbonilo, hidroxi y (NR^eR^f)carbonilo; estando el heterociclilo además opcionalmente sustituido con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "$-NR^eR^f$," tal como se usa en el presente documento, se refiere a dos grupos, R^e y R^f, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^e y R^f están seleccionados independientemente de

hidrógeno, alquilo, arilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, (cicloalquil)alquilo no sustituido, heterociclilo no sustituido, heterociclilalquilo no sustituido, (NR^xR^y)alquilo y (NR^xR^y)carbonilo.

El término "(NR^eR^f)alquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^eR^f$.

El término "(NR^eR^f)alquilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo (NR^eR^f)alquilo unido a un resto molecular principal a través de un grupo carbonilo.

El término "(NR^eR^f)carbonilo," tal como se usa en el presente documento, se refiere a un grupo $-NR^eR^f$ unido al resto molecular principal a través de un grupo carbonilo.

El término "(NR^eR^f)sulfonilo," tal como se usa en el presente documento, se refiere a un grupo $-NR^eR^f$ unido al resto molecular principal a través de un grupo sulfonilo.

El término "$-NR^xR^y$," tal como se usa en el presente documento, se refiere a dos grupos, R^x y R^y, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^x y R^y están seleccionados independientemente de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo no sustituido, arilalcoxicarbonilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, heterociclilo no

sustituido y $(NR^{x'}R^{y'})$carbonilo, seleccionándose $R^{x'}$ y $R^{y'}$ independientemente de hidrógeno y alquilo.

El término "(NR^xR^y)alquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^xR^y$.

El término "(NR^xR^y)carbonilo," tal como se usa en el presente documento, se refiere a un grupo $-NR^xR^y$ unido al resto molecular principal a través de un grupo carbonilo.

El término "$-NR^xR^y$," tal como se usa en el presente documento, se refiere a dos grupos, R^x y R^y, que están unidos al resto molecular principal a través de un átomo de nitrógeno. R^x y R^y están seleccionados independientemente de hidrógeno y alquilo.

El término "$(NR^{x'}R^{y'})$carbonilo," tal como se usa en el presente documento, se refiere a un grupo $-NR^{x'}R^{y'}$ unido al resto molecular principal a través de un grupo carbonilo.

El término "oxo", como se usa en el presente documento, se refiere a =O.

El término "sulfonilo", tal como se usa en el presente documento, se refiere a $-SO_2-$.

Existen centros asimétricos en los compuestos de la presente descripción. Estos centros se designan con los símbolos "R" o "S", dependiendo de la configuración de los sustituyentes alrededor del átomo de carbono quiral. Debe entenderse que la descripción engloba todas las formas

isoméricas estereoquímicas, o sus mezclas, que poseen la capacidad de inhibir NS5A. Se pueden preparar estereoisómeros individuales de los compuestos sintéticamente a partir de materiales iniciales comercialmente disponibles que contienen centros quirales o por preparación de mezclas de productos enantioméricos seguido de separación como por ejemplo conversión a una mezcla de diastereómeros seguido de separación o recristalización, técnicas cromatográficas o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de estereoquímica particular, bien están comercialmente disponibles o bien se pueden preparar y resolver mediante técnicas conocidas en la técnica.

Ciertos compuestos de la presente descripción pueden existir también en formas conformacionales estables diferentes que pueden ser separables. La asimetría torsional debida a rotación restringida sobre un enlace individual asimétrico, por ejemplo debido a su impedimento estérico o tensión de anillo, puede permitir la separación de conformadores diferentes. La presente descripción incluye cada isómero conformacional de estos compuestos y mezclas de los mismos.

Los compuestos de la presente descripción también existen como tautómeros; por tanto la presente descripción también incluye formas tautoméricas.

La expresión "compuestos de la presente descripción" y expresiones equivalentes, pretenden incluir compuestos de Fórmula (I), y sus enantiómeros, diastereoisómeros y sales farmacéuticamente aceptables. De forma similar, las referencias a los intermedios se pretende que engloben sus sales cuando el contexto lo permita.

Se pretende que la presente descripción incluya todos los isótopos de los átomos que aparecen en los presentes compuestos. Los isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. Como ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Los compuestos marcados con isótopos de la invención generalmente se pueden preparar por técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en el presente documento, usando un reactivo marcado con isótopo apropiado en lugar del reactivo no marcado que se usa en otros casos. Tales compuestos pueden tener una diversidad de usos potenciales, por ejemplo como estándares y reactivos en determinación de actividad biológica. En el caso de los isótopos estables, los compuestos pueden tener el potencial de modificar favorablemente propiedades biológicas, farmacológicas o farmacocinéticas.

Los compuestos de la presente descripción pueden

existir como sales farmacéuticamente aceptables. La expresión “sal farmacéuticamente aceptable”, como se usa en el presente documento, representa sales o formas híbridas de los compuestos de la presente descripción que son solubles en agua o solubles en aceite o dispersables, que son, dentro del alcance del juicio médico bien fundamentado, adecuadas para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica, u otro problema o complicación es proporcional con una relación beneficio/riesgo razonable, y son efectivos para su uso deseado. Las sales se pueden preparar durante el aislamiento y purificación finales de los compuestos o por separado haciendo reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Las sales de adición de ácido representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, canforato, canforsulfonato; digluconato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluenosulfonato y undecanoato.

Ejemplos de ácidos que se pueden usar para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico y fosfórico, y ácidos orgánicos tales como ácido oxálico, maleico, succínico y cítrico.

Las sales de adición básica se pueden preparar durante el aislamiento y la purificación finales de los compuestos haciendo reaccionar un grupo carboxilo con una base adecuada tal como el hidróxido, carbonato, o bicarbonato de un catión metálico o con amoniaco o una amina primaria, secundaria, o terciaria. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio y aluminio, así como cationes de amina cuaternario no tóxicos tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, diciclohexilamina, procaína, dibencilamina, N,N-dibencilfenetilamina y N,N'-dibenciletilendiamina. Otras aminas orgánicas representativas útiles para la formación de sales de adición básicas incluyen etilendiamina, etanolamina, dietanolamina, piperidina y piperazina.

Cuando es posible que, para uso en terapia, se puedan administrar cantidades terapéuticamente eficaces de un compuesto de Fórmula (I), así como sus sales

farmacéuticamente aceptables, en forma de compuestos químicos en bruto, es posible presentar el ingrediente activo como una composición farmacéutica. Por consiguiente, la descripción proporciona además composiciones farmacéuticas que incluyen cantidades terapéuticamente eficaces de compuestos de Fórmula (I) o sus sales farmacéuticamente aceptables, y uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. La expresión "cantidad terapéuticamente eficaz," tal como se usa en el presente documento, se refiere a la cantidad total de cada ingrediente activo que es suficiente para mostrar un beneficio significativo al paciente, por ejemplo, una reducción mantenida de la carga vírica. Cuando se aplica a un principio activo individual, administrado solo, el término se refiere a ese ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los principios activos que provoca el efecto terapéutico, ya se administren combinados, en serie o de forma simultánea. Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables, son tal como se han descrito con anterioridad. El/los portador(es), diluyente(s), o excipiente(s) deben ser aceptables en el sentido de que sean compatibles con los otros ingredientes de la formulación y no deletéreos para el receptor de los mismos. De acuerdo con otro aspecto de la presente descripción se proporciona también un procedimiento para la

preparación de una formulación farmacéutica que incluye mezclar un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable", tal como se usa en el presente documento, se refiere a los compuestos, materiales, composiciones y/o formas farmacéuticas que son, dentro del alcance del criterio médico habitual, adecuados para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación acorde con una relación beneficio/riesgo razonable, y son eficaces para su uso deseado.

Las formulaciones farmacéuticas pueden presentarse en formas monodosis que contienen una cantidad predeterminada de principio activo por monodosis. En una monoterapia para la prevención y tratamiento de enfermedad mediada por VHC son típicos niveles de dosis que varían de aproximadamente 0.01 a aproximadamente 250 miligramos por kilogramo ("mg/kg") de peso corporal por día, con preferencia de aproximadamente 0.05 a aproximadamente 100 mg/kg de peso corporal por día de los compuestos de la presente descripción. Habitualmente, las composiciones farmacéuticas de la presente descripción se administrarán desde aproximadamente 1 a aproximadamente 5 veces al día o de forma alternativa, en forma de infusión

continua. La administración puede usarse como terapia crónica o aguda. La cantidad de principio activo que puede combinarse con los materiales portador para producir una única forma farmacéutica variará dependiendo de la afección que se esté tratando, de la gravedad de la afección, del tiempo de administración, la vía de administración, la velocidad de excreción del compuesto usado, la duración del tratamiento y la edad, sexo, peso y afección del paciente. Las formulaciones monodosis son las que contienen una dosis o subdosis diaria, tal como se indica anteriormente en el presente documento, o una fracción apropiada de las mismas de un principio activo. Generalmente, el tratamiento se inicia con dosis pequeñas sustancialmente por debajo de la dosis óptima del compuesto. Después, la dosis se aumenta en pequeños incrementos hasta que se alcanza el efecto óptimo en las circunstancias dadas. En general, el compuesto se administra, de la forma más deseable a un nivel de concentración que generalmente conseguirá resultados antiviralmente eficaces sin provocar efectos secundarios dañinos ni perjudiciales.

Cuando las composiciones de esta descripción comprenden una combinación de un compuesto de la presente descripción y uno o más agentes terapéuticos o profilácticos adicionales, tanto el compuesto como el agente adicional habitualmente están presentes a niveles de dosis de

aproximadamente 10 a 150%, y más preferentemente entre aproximadamente 10 y 80% de la dosis que normalmente se administra en una pauta de monoterapia.

Las formulaciones farmacéuticas se pueden adaptar para administración por cualquier vía apropiada, por ejemplo por la vía oral (incluyendo la bucal o la sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual, o transdérmica), vaginal, o parenteral (incluyendo inyecciones o infusiones subcutáneas, intracutáneas, intramusculares, intraarticulares, intrasinoviales, intraesternales, intratecales, intralesionales, intravenosas, o intradérmicas). Tales formulaciones se pueden preparar por cualquier procedimiento conocido en la técnica de farmacia, por ejemplo por unión en asociación el ingrediente activo con el/los portador(es) o excipiente(s). Son preferentes la administración oral o la administración mediante inyección.

Las formulaciones farmacéuticas adaptadas para administración oral pueden presentarse como unidades discretas tales como cápsulas o comprimidos; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; o emulsiones de aceite-en-agua o emulsiones de agua-en-aceite.

Por ejemplo, para administración oral en la forma de un comprimido o una cápsula, el componente de fármaco activo se puede combinar con un portador inerte

farmacéuticamente aceptable no tóxico, oral tal como etanol, glicerol, agua y similares. Los polvos se prepararon moliendo el compuesto a un tamaño fino adecuado y mezclando con un portador farmacéutico molido de forma similar tal como un carbohidrato comestible, como, por ejemplo, almidón o manitol. También pueden estar presentes agente aromatizante, conservante, dispersante y colorante.

Las cápsulas se hacen preparando una mezcla en polvo, como se describe anteriormente y cubiertas de gelatina formadas cargadas. Se pueden añadir agentes deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio, o polietilenglicol sólido a la mezcla en polvo antes de la operación de carga. Un agente disgregante o solubilizante tal como agar-agar, carbonato de calcio, o carbonato de sodio puede también añadirse para incrementar la disponibilidad del medicamento cuando la cápsula es ingerida.

Además, cuando se desee o sea necesario, también pueden incorporarse aglutinantes, lubricantes, agentes disgregantes y agentes colorantes adecuados a la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como goma arábiga, goma de tragacanto o alginato sódico, carboximetilcelulosa, polietilenglicol y similares. Los lubricantes usados en

estas formas de dosificación incluyen oleato de sodio, cloruro de sodio y similares. Los disgregadores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana, y similares. Los comprimidos se formularon, por ejemplo, preparando un mezcla en polvo, granulando o soldando con fusión incompleta, añadiendo un lubricante y disgregante, y prensando en comprimidos. Se preparó una mezcla en polvo mezclando el compuesto, molido adecuadamente, con un diluyente o base como se describe anteriormente, y opcionalmente, con un ligando tal como carboximetilcelulosa, un alginato, galatina, o polivinilpirrolidina, un retardante de solución tal como parafina, un acelerador de resorción tal como una sal cuaternaria y/o agente de absorción tal como bentonita, caolín o fosfato dicálcico. La mezcla en polvo se puede granular por humectación con un aglutinante tal como jarabe, pasta de almidón, mucílago de goma arábiga, o soluciones de materiales celulósicos o poliméricos y forzándola a pasar a través de un tamiz. Como una alternativa para granular, la mezcla en polvo puede hacerse pasar por la máquina compresora y el resultado son postas formadas imperfectamente rotas en gránulos. Los gránulos se pueden lubricar para evitar que se adhieran al comprimido formando moldes por medio de la adición de ácido esteárico, una sal de estearato, talco, o aceite mineral. La mezcla lubricada se comprime después en comprimidos. Los compuestos

de la presente descripción se pueden combinar también con un portador inerte que fluye libre y se pueden comprimir en comprimidos directamente sin ir a través de las etapas de granulación o formación de postas. Se pueden proporcionar un revestimiento protector transparente u opaco constituido por un revestimiento sellante de goma laca, un revestimiento de azúcar o de material polimérico, y un revestimiento pulido de cera. Se pueden añadir tintes a estos recubrimientos para distinguir dosificaciones unitarias diferentes.

Los fluidos orales tales como una solución, jarabes y elixires se pueden preparar en forma de dosificación unitaria tal que una cantidad dada contiene una cantidad predeterminada del compuesto. Los jarabes se pueden preparar disolviendo el compuesto en una solución acuosa adecuadamente aromatizada, mientras que se prepararon elixires por el uso de un portador no tóxico. Se pueden añadir también solubilizantes y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de polioxietileno sorbitol, conservantes, aditivo aromático tal como aceite de menta o edulcorantes naturales, o sacarina u otros edulcorantes artificiales y similares.

Donde sea apropiado, se pueden microencapsular las formulaciones de dosificación unitaria para administración oral. La formulación se pueden preparar también para prolongar o mantener la liberación como por ejemplo

revistiendo o incrustando material particulado en polímeros, ceras, o similares.

Los compuestos de la Fórmula (I), y sus sales farmacéuticamente aceptables, también pueden administrarse en forma de sistemas de administración de liposomas, tales como vesículas unilaminares, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formar a partir de una diversidad de fosfolípidos, tales como colesterol, estearilamina, o fosfatidilcolinas.

Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables también pueden administrarse usando anticuerpos monoclonales como portadores individuales a los que se acoplan las moléculas de compuesto. Los compuestos pueden estar acoplados también con polímeros solubles como transportadores de fármacos marcables como objetivos. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol, o polietilenóxidopolilisina sustituida con residuos de palitoílo. Además, los compuestos pueden acoplarse a una clase de polímeros biodegradables útiles en lograr liberación controlada de un fármaco, por ejemplo, ácido poliláctico, caprolactona poliépsilon, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos, y copolímeros de

bloque de hidrogeles reticulados o anfipáticos.

Las formulaciones farmacéuticas adaptadas para administración transdérmica pueden presentarse como parches discretos que se desea que permanezcan en contacto íntimo con la epidermis de un receptor durante un periodo de tiempo prolongado. Por ejemplo, el ingrediente activo puede liberarse del parche por iontoforesis como se describe de forma general en *Pharmaceutical Research*, *3*(6):318 (1986).

Las formulaciones farmacéuticas adaptadas para administración tópica se pueden formular como pomadas, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, pulverizaciones, aerosoles o aceites.

Para tratamientos del ojo o de otros tejidos externos, por ejemplo boca y piel, las formulaciones se aplican preferentemente como una pomada o crema tópica. Cuando se formula en una pomada, el ingrediente activo se puede usar bien con una base parafínica o bien con una base de pomada mezclable en agua. Alternativamente, el ingrediente activo se puede formular en una crema con una base de aceite-en-agua o con una base de agua-en-aceite.

Las formulaciones farmacéuticas adaptadas para administraciones tópicas para el ojo incluyen gotas oculares en las que el ingrediente activo se disuelve o suspende en un portador adecuado, especialmente un disolvente acuoso.

Las formulaciones farmacéuticas adaptadas para

administración tópica en la boca incluyen tabletas, pastillas y enjuagues bucales.

Las formulaciones farmacéuticas adaptadas para administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para administración nasal en las que el portador es un sólido incluyen un polvo grueso que tiene un tamaño de partículas de por ejemplo en el intervalo de 20 a 500 micrómetros que se administra en la forma en que se toma rape, es decir, por inhalación rápida a través de la vía nasal desde un recipiente de polvo mantenido próximo a la nariz. Las formulaciones adecuadas en las que el transportador es un líquido, para administración como una aspersión nasal o como gotas nasales, incluyen soluciones acuosas o soluciones aceitosas del ingrediente activo.

Las formulaciones adaptadas para administración por inhalación incluyen espolvoreados o neblinas de partículas finas, que se pueden generar por medio de diversos tipos de aerosoles, nebulizadores, o insufladores presurizados en dosis medidas.

Las formulaciones farmacéuticas adaptadas para administración vaginal pueden presentarse como pesarios, tampones, cremas, geles, pastas, espumas o formulaciones de aspersión.

Las formulaciones farmacéuticas adaptadas para administración parenteral incluyen soluciones de inyección estériles acuosas y no acuosas que pueden contener anti-oxidantes, reguladores de pH, bacteriostáticos y solutos que vuelven a la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes en suspensión y agentes espesantes. Las formulaciones pueden presentarse en recipientes de dosis unitaria o de multidosis, por ejemplo ampollas y viales sellados, y pueden almacenarse en una condición secada por congelación (liofilizada) que requiere sólo la adición del transportador líquido estéril, por ejemplo agua para inyecciones, inmediatamente antes de usar. Se pueden preparar soluciones y suspensiones de inyección extemporáneas a partir de polvos estériles, gránulos y comprimidos.

Debería entenderse que además de los ingredientes mencionados en particular anteriormente, las formulaciones pueden incluir otros agentes convencionales en la técnica que se han considerado para el tipo de formulación en cuestión, por ejemplo aquellos adecuados para administración oral pueden incluir agentes aromatizantes.

El término “paciente” incluye seres humanos y otros mamíferos.

El término “tratar” se refiere a: (i)

prevenir la aparición de una enfermedad, trastorno o estado patológico en un paciente que puede estar predispuesto a la enfermedad, trastorno y/o estado patológico pero al que todavía no se le ha diagnosticado que lo tiene; (ii) inhibir la enfermedad, trastorno o estado patológico, es decir, detener su desarrollo; y (iii) aliviar la enfermedad, trastorno o estado patológico, es decir, causando la regresión de la enfermedad, trastorno y/o estado patológico.

Los compuestos de la presente descripción también se pueden administrar con una ciclosporina, por ejemplo, ciclosporina A. Se ha demostrado que la ciclosporina A es activa contra el VHC en ensayos clínicos (*Hepatology* **2003**, *38*, 1282; *Biochem. Biophys. Res. Commun.* **2004**, *313*, 42; *J. Gastroenterol.* **2003**, *38*, 567).

La Tabla 1 a continuación enumera algunos ejemplos ilustrativos de compuestos que se pueden administrar con los compuestos de esta descripción. Los compuestos de la descripción se pueden administrar con otros compuestos con actividad contra el VHC en terapia de combinación, bien de forma conjunta o por separado o combinando los compuestos para formar una composición.

Tabla 1

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
NIM811 Debio-025		Inhibidores de ciclofilina	Novartis Debiopharm
Zadaxin		Inmunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista de TLR9	Coley
Batabulin (T67)	Anticanceroso	βInhibidor de β- tubulina	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	Antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	Antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	Inhibidor del VHC	Achillion / Gilead
Compuestos y sales de pirazolopirimidina Del documento WO2005/047288 26 de mayo de 2005	Antiviral	Inhibidores del VHC	Arrow Therapeutics Ltd.

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Levovirina	Antiviral	Inhibidor de IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	Inhibidor de IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	Anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Israel
Telaprevir (VX-950, LY-570310)	Antiviral	Inhibidor de la serina proteasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly y Co. Inc., Indianapolis, IN
HCV-796	Antiviral	Inhibidor de la replicasa NS5B	Wyeth / Viropharma
NM-283	Antiviral	Inhibidor de la replicasa NS5B	Idenix / Novartis
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis
GL-60667	Antiviral	Inhibidor de la replicasa NS5B	Gene Labs / Novartis

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
2'C MeA	Antiviral	Inhibidor de la replicasa NS5B	Gilead
PSI6130	Antiviral	Inhibidor de la replicasa NS5B	Roche
R1626	Antiviral	Inhibidor de la replicasa NS5B	Roche
2'C Metil adenosina	Antiviral	Inhibidor de la replicasa NS5B	Merck
JTK-003	Antiviral	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirina	Antiviral	Ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirina	Antiviral	Ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Viramidina	Antiviral	Profármaco de ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	Ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Inhibidor de serina proteasas	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antiviral	Inhibidor de serina proteasas	Schering Plough

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Zadazim	Inmunomodulador	Inmunomodulador	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomodulador	Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Inmunosupresor	Inmunosupresor de IgG del VHC	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunosupresor	Inmunosupresor de IgG del VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferón	IFN-α2b de albúmina	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferón	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferón	IFN-ω	Intarcia Therapeutics
IFN-β y EMZ701	Interferón	IFN-β y EMZ701	Transition Therapeutics Inc., Ontario, Canadá
Rebif	Interferón	IFN-β1a	Serono, Ginebra, Suiza

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Rebif	Interferón	IFN-β1a	Serono, Ginebra, Suiza
Roferon A	Interferón	IFN-α2a	F. Hoffmann-La Roche LTD, Basilea, Suiza
Intrón A	Interferón	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intrón A y Zadaxin	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharma. Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferón	IFN-α2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferón	INF-γ	InterMune Inc., Brisbane, CA
Interferón-β	Interferón	Interferón-β-1a	Serono

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
Multiferon	Interferón	IFN de acción prolongada	Viragen / Valentis
Wellferon	Interferón	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, Reino Unido
Omniferon	Interferón	IFN-α natural	Viragen Inc., Plantation, FL
Pegasys	Interferón	IFN-α2a pegilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ceplene	Interferón	IFN-α2a PEGilado / modulador inmunológico	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys y Ribavirina	Interferón	IFN-α2a pegilado/ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza
PEG-Intrón	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intrón / ribavirina	Interferón	IFN-α2b PEGilado/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protección hepática	Antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protección hepática	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
ITMN-191 (R-7227)	Antiviral	Inhibidor de serina proteasas	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de la replicasa NS5B	Genelabs
ANA-971	Antiviral	Agonista de TLR-7	Anadys
Boceprevir	Antiviral	Inhibidor de serina proteasas	Schering Plough
TMS-435	Antiviral	Inhibidor de serina proteasas	Tibotec BVBA, Mechelen, Bélgica
BI-201335	Antiviral	Inhibidor de serina proteasas	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
MK-7009	Antiviral	Inhibidor de serina proteasas	Merck
PF-00868554	Antiviral	Inhibidor de replicasas	Pfizer
ANA598	Antiviral	Inhibidor no nucleosídico de polimerasa NS5B	Anadys Pharmaceuticals, Inc., San Diego, CA, USA
IDX375	Antiviral	Inhibidor no nucleosídico de replicasa	Idenix Pharmaceuticals, Cambridge, MA, USA

Nombre comercial	*Clase fisiológica*	*Tipo de inhibidor o diana*	*Compañía suministradora*
BILB 1941	Antiviral	Inhibidor de polimerasa NS5B	Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canadá
PSI-7851	Antiviral	Inhibidor nucleosídico de polimerasa	Pharmasset, Princeton, NJ, USA
VCH-759	Antiviral	Inhibidor de polimerasa NS5B	ViroChem Pharma
VCH-916	Antiviral	Inhibidor de polimerasa NS5B	ViroChem Pharma
GS-9190	Antiviral	Inhibidor de polimerasa NS5B	Gilead
Peg-interferón lambda	Antiviral	Interferón	ZymoGenetics / Bristol-Myers Squibb

Los compuestos de la presente descripción también se pueden usar como reactivos de laboratorio. Los compuestos pueden ser una contribución decisiva para proporcionar herramientas de investigación para diseñar ensayos de replicación del virus, validación de sistemas de ensayo en animales y estudios de biología estructural para potenciar más el conocimiento de los mecanismos de la enfermedad por VHC. Además, los compuestos de la presente descripción son

útiles para establecer o determinar el sitio de unión de otros compuestos antivirales, por ejemplo, por inhibición competitiva.

Los compuestos de esta descripción también pueden ser útiles para tratar o prevenir contaminación viral de materiales y por tanto reducir el riesgo de infección viral de laboratorio o personal médico o pacientes que entren en contacto con tales materiales, por ejemplo, sangre, tejidos, instrumental y prendas quirúrgicas, instrumental y prendas de laboratorio, y aparatos y materiales para la extracción o transfusión de sangre.

Esta descripción pretende incluir compuestos que tienen la Fórmula (I) cuando se preparan por procedimientos de síntesis o por procedimientos metabólicos que incluyen los que se producen en el cuerpo humano o animal (*in vivo*) o procedimientos que se producen *in vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo en particular en los ejemplos ilustrativos siguientes, son bien conocidas por los expertos en la técnica. Algunas de las abreviaturas usadas son las siguientes: aprox, durante unos; min para minutos; h o hr para horas; ta o TA para la temperatura ambiente Tr para tiempo de retención; T_r para el tiempo de retención; TFA para ácido trifluoroacético; DMSO para dimetilsulfóxido; Me para metilo; THF para tetrahidrofurano; *t*-Bu o t-Bu para *terc*-

butilo; EDCI para 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato; DMAP para 4-dimetilaminopiridina; DBU para 1,8-diazabicicloundec-7-eno; Ph para fenilo; DEA para dietilamina; Et para etilo; DMF para N,N-dimetilformamida; OAc para acetato; HMDS para hexametildisilano; pTsOH para ácido paratoluenosulfónico; iPr_2EtN, DIEA, o DIPEA para diisopropiletilamina; EtOAc o EtOAc o EA para acetato de etilo; Et_3SiH para trietilsilano; MeOH para metanol; $TMSCHN_2$ para trimetilsilildiazometano; H-D-Ser-OBzl.HCl para D-serina bencilo éster clorhidrato; EtOH para etanol; Me_2 para dimetilsulfuro; TEA o Et_3N para trietilamina; LiHMDS para hexametildisilazida de litio; DIBAL para hidruro de diisobutilaluminio; TBDMS-Cl para cloruro de terc-butildimetilsililo; i-PrOH para isopropanol; Boc, boc, o BOC para terc-butoxicarbonilo; Cbz-Cl para cloroformiato de bencilo; Bn para bencilo; DEAD para dietilazodicarboxilato; mCPBA para ácido meta-cloroperoxibenzoico; DCM para diclorometano; TMSCN para cianuro de trimetilsililo; ACN o MECN para acetonitrilo; DPPPE para 1,5-bis(difenilfosfino)pentano; TMEDA para tetrametiletilendiamina; DMA para N,N-dimetilacetamida; MeOD para CD_3OD; Hex para hexanos; NaOEt para etóxido sódico; MTBE para metil terc butil éter; NCS para N-clorosuccinimida; Et_2O para éter dietílico; DME para 1,2-dimetoxietano; y EEDQ para N-etoxicarbonil-2-etoxi-1,2-dihidroquinolina.

La presente descripción se describirá ahora en relación con determinadas modalidades que no se pretende que limiten su alcance. Por el contrario, la presente descripción abarca todas las alternativas, modificaciones y equivalentes y que puedan incluirse dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, que incluyen modalidades específicas, ilustrarán una práctica de la presente descripción, entendiéndose que los ejemplos son para fines de ilustración de determinadas modalidades y se presentan para proporcionar lo que se cree que es la descripción más útil y fácilmente entendible de sus procedimientos y aspectos conceptuales.

Los materiales de partida pueden obtenerse de fuentes comerciales o prepararse mediante procedimientos ya establecidos en la bibliografía conocidos por las personas expertas en la técnica.

SÍNTESIS DE CAPS COMUNES

Condiciones de análisis de los compuestos

La valoración de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema de CL Shimadzu CL acoplado con un sistema de EM Waters MICROMASS® ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Condiciones adicionales de CL aplicables a la presente sección, a no ser que se indique de otro modo.

Condiciones de EM-W1

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W2

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones de EM-W5

Columna = XTERRA® 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 30

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones-D1

Columna = XTERRA® C18 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones-D2

Columna = PHENOMENEX® Luna 4.6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condiciones-M3

Columna = XTERRA® C18 3.0 X 50 mm S7

% Inicial de B = 0

% Final de B = 40

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición I

Columna = PHENOMENEX® Luna 3.0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición II

Columna = PHENOMENEX® Luna 4.6X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de parada = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Condición III

Columna = HPLC XTERRA® C18 3.0 x 50mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de parada = 4 min

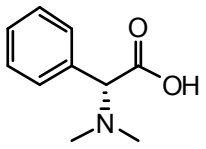
Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = TFA al 0.1% en metanol al 10%/H_2O al 90%

Disolvente B = TFA al 0.1% en metanol al 90%/H_2O al 10%

Cap-1

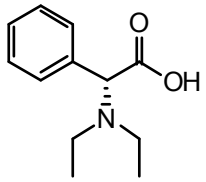


Ácido (R)-2-(dimetilamino)-2-fenilacético

Se añadió una suspensión de Pd al 10%/C (2.0 g) en metanol (10 ml) a una mezcla de (R)-2-fenilglicina (10 g, 66.2 mmol), formaldehído (33 ml de 37% en peso en agua), HCl 1N (30 ml) y metanol (30 ml) y se expuso a H_2 (413.57 kPa) durante 3 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de Cap-1 como agujas blancas (4.0 g). Rotación óptica: -117.1° [c = 9.95 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); CL (Condición I): T_R = 0.25; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$

180.10; encontrado 180.17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; encontrado 180.1017.

Cap-2

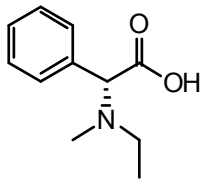


Ácido (R)-2-(dietilamino)-2-fenilacético

Se añadió $NaBH_3CN$ (6.22 g, 94 mmol) en porciones durante unos pocos minutos a una mezcla enfriada (hielo/agua) de (R)-2-fenilglicina (6.02 g, 39.8 mmol) y MeOH (100 ml), y se agitó durante 5 min. Se añadió acetaldehído (10 ml) gota a gota durante 10 minutos y se continuó agitando a la misma temperatura fría durante 45 minutos y a temperatura ambiente durante ~6.5 horas. La mezcla de reacción se volvió a enfriar con baño de hielo-agua, se trató con agua (3 ml) y luego se inactivó con una adición gota a gota de HCl concentrado durante ~ 45 min hasta que el pH de la mezcla fue ~ 1.5-2.0. El baño de enfriamiento se retiró y se continuó agitando mientras se añadía HCl concentrado con el fin de mantener el pH de la mezcla aproximadamente a 1.5-2.0. La mezcla de reacción se agitó durante una noche, se filtró para separar la suspensión blanca y el filtrado se concentró a vacío. El material bruto se recristalizó en etanol proporcionando la sal HCl de Cap-2 como un sólido blanco brillante en dos tandas (tanda-1: 4.16 g; tanda-2: 2.19 g). RMN de ^1H (DMSO-d_6,

δ = 2.5 ppm, 400 MHz): 10.44 (1.00, s ancho, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (m ancho, 2H), 2.98 (m ancho, 2H), 1.20 (s ancho aparente, 6H). Tanda-1: $[\alpha]^{25}$ -102.21° (c = 0.357, H_2O); canda-2: $[\alpha]^{25}$ -99.7° (c = 0.357, H_2O). CL (Condición I): T_R = 0.43 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; encontrado 208.26

Cap-3

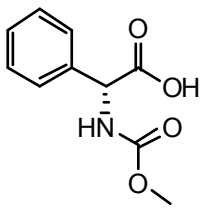


Se añadió secuencialmente acetaldehído (5.0 ml, 89.1 mmol) y una suspensión de Pd al 10%/C (720 mg) en metanol/H_2O (4 ml/1 ml) a una mezcla enfriada (~ 15 °C) de (R)-2-fenilglicina (3.096g, 20.48 mmol), HCl 1N (30 ml) y metanol (40 ml). Se retiró el baño de enfriamiento y la mezcla de reacción se agitó bajo un globo de H_2 durante 17 horas. Se añadió más acetaldehído (10 ml, 178.2 mmol) y se continuó agitando en atmósfera de H_2 durante 24 horas [Nota: el suministro de H_2 se reponía cuando era necesario a través de la reacción]. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante

(2.846 g). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 14.15 (s ancho, 1H), 9.55 (s ancho, 2H), 7.55-7.48 (m, 5H), 2.88 (m ancho, 1H), 2.73 (m ancho, 1H), 1.20 (t aparente, J = 7.2, 3H). CL (Condición I): T_R = 0.39 min; índice de homogeneidad >95%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; encontrado 180.18.

Se añadió una suspensión de Pd al 10%/C (536 mg) en metanol/H_2O (3 ml/1 ml) a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1.492 g, 6.918 mmol), formaldehído (20 ml de 37% en peso en agua), HCl 1N (20 ml) y metanol (23 ml). La mezcla de reacción se agitó bajo un globo de H_2 durante ~72 horas, en el que se el suministro de H_2 se reanudaba según se necesitaba. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol (50 ml) proporcionando la sal HCl de Cap-3 como un sólido blanco (985 mg). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 10.48 (s ancho, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (s ancho aparente, 2H), 2.65 (s ancho, 3H), 1.24 (m ancho, 3H). CL (Condición I): T_R = 0.39 min; índice de homogeneidad >95%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; encontrado 194.18; EMAR: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; encontrado 194.1181.

Cap-4



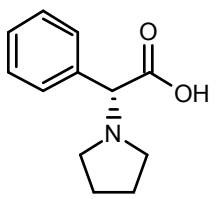
Ácido (R)-2-(metoxicarbonilamino)-2-fenilacético

Se añadió $ClCO_2Me$ (3.2 ml, 41.4 mmol) gota a gota a una semisolución en THF enfriada (hielo/agua) (410 ml) de 2-amino-2-fenilacetato de (R)-*terc*-butilo/HCl (9.877 g, 40.52 mmol) y diisopropiletilamina (14.2 ml, 81.52 mmol) durante 6 min, y se agitó a una temperatura similar durante 5.5 horas. El componente volátil se eliminó a vacío, y el residuo se repartió entre agua (100 ml) y acetato de etilo (200 ml). La fase orgánica se lavó con HCl 1N (25 ml) y solución saturada de $NaHCO_3$ (30 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío. El aceite resultante incoloro se trituró en hexanos, se filtró y se lavó con hexanos (100 ml) proporcionando 2-(metoxicarbonilamino)-2-fenilacetato de (R)-*terc*-butilo como un sólido blanco (7.7 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.98 (d, J = 8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J = 8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). CL (Condición I): T_R = 1.53 min; índice de homogeneidad ~90 %; CL-EM: Anal. Calculado para $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; encontrado 288.15.

Se añadió TFA (16 ml) gota a gota a una solución enfriada (hielo/agua) en CH_2Cl_2 (160 ml) del producto anterior durante 7 minutos y se retiró el baño de enfriamiento y la

mezcla de reacción se agitó durante 20 horas. Puesto que la desprotección todavía no fue completa, se añadió más TFA (1.0 ml) y se continuó agitando durante otras 2 horas más. El componente volátil se eliminó a vacío, y el residuo oleoso resultante se trató con éter dietílico (15 ml) y hexanos (12 ml) proporcionando un precipitado. El precipitado se filtró y se lavó con éter dietílico/hexanos (relación ~1:3; 30 ml) y se secó a vacío proporcionando Cap-4 como un sólido blanco apelusado (5.57 g). Rotación óptica: -176.9° [c = 3.7 mg/ml en H_2O; λ = 589 nm]. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.84 (s ancho, 1H), 7.96 (d, J = 8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, J = 8.3, 1H), 3.55 (s, 3H). CL (Condición I): T_R = 1.01 min; índice de homogeneidad >95%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; encontrado 210.17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; encontrado 210.0756.

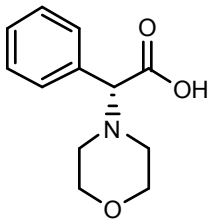
Cap-5



Se calentó a 100°C durante 21 horas una mezcla de (R)- 2-fenilglicina (1.0 g, 6.62 mmol), 1,4-dibromobutano (1.57 g, 7.27 mmol) y Na_2CO_3 (2.10 g, 19.8 mmol) en etanol (40 ml). La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró, y el filtrado se concentró a vacío. El residuo se disolvió en etanol y se acidificó con HCl

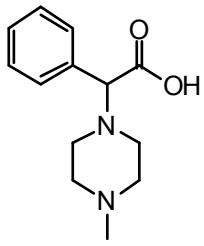
1N hasta pH 3-4, y el componente volátil se eliminó a vacío. El material bruto resultante se purificó por una HPLC de fase inversa (agua/metanol/TFA) proporcionando la sal TFA de Cap-5 como una espuma blanca semiviscosa (1.0 g). RMN de ^{1}H (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (s ancho, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (s ancho aparente, 2H), 3.05 (s ancho aparente, 2H), 1.95 (s ancho aparente, 4H); T_R = 0.30 min (Cond. I); índice de homogeneidad >98%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; encontrado 206.25.

Cap-6



La sal TFA de Cap-6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el procedimiento de preparación de Cap-5. RMN de ^{1}H (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.20 (s ancho, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (s ancho aparente, 4H), 3.08 (s ancho aparente, 2H), 2.81 (s ancho aparente, 2H); T_R = 0.32 min (Condición I); >98%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; encontrado 222.20; EMAR: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; encontrado 222.1121.

Cap-7



Cap-7a: enantiómero-1
Cap-7b: enantiómero-2

Se añadió gota a gota una solución en CH_2Cl_2 (200 ml) de cloruro de p-toluenosulfonilo (8.65 g, 45.4 mmol) a una solución (-5 °C) en CH_2Cl_2 (200 ml) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10.0 g, 41.3 mmol), trietilamina (5.75 ml, 41.3 mmol) y 4-dimetilaminopiridina (0.504 g, 4.13 mmol), mientras se mantenía la temperatura de -5 °C a 0 °C. La reacción se agitó a 0 °C durante 9 horas, y luego se almacenó en un congelador (-25 °C) durante 14 horas. Se dejó descongelar hasta temperatura ambiente y se lavó con agua (200 ml), HCl 1N (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso que solidificó en reposo (16.5 g). La integridad quiral del producto no se verificó y el producto se usó en la etapa siguiente sin purificación adicional. RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.78 (d, J = 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, J = 12.5, 1H), 5.10 (d, J = 12.5, 1H), 2.39 (s, 3H). T_R = 3.00 (Condición III); índice de homogeneidad >90%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; encontrado 419.04.

Se calentó a 65°C durante 7 horas una solución en THF (75 ml) de 2-fenil-2-(tosiloxi)acetato de bencilo (6.0 g, 15.1 mmol), 1-metilpiperazina (3.36 ml, 30.3 mmol) y N,N-diisopropiletilamina (13.2 ml, 75.8 mmol). Se dejó enfriar la reacción hasta temperatura ambiente y el componente volátil se eliminó a vacío. El residuo se repartió entre acetato de etilo y agua, y la fase orgánica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó por cromatografía ultrarrápida (gel de sílice, etilo acetato) proporcionando 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso anaranjado-pardo (4.56 g). El análisis HPLC quiral (CHIRALCEL®OD-H) indicó que la muestra es una mezcla de estereoisómeros en una relación 38.2 a 58.7. La separación de los estereoisómeros se realizó como sigue: se disolvió el producto en 120 ml de etanol/heptano (1:1) y se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluyendo con 85:15 Heptano/etanol a 75 ml/min, y se controló a 220 nm. El estereoisómero-1(1.474 g) y el estereoisómero-2 (2.2149 g) se recuperaron como aceite viscoso. RMN de ^1H ($CDCl_3$, δ = 7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, J = 12.5, 1H), 5.08 (d, J = 12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (s ancho aparente, 8H), 2.25 (s, 3H). T_R = 2.10 (Condición III); índice de homogeneidad >98%; CL-EM: Anal. Calculado para

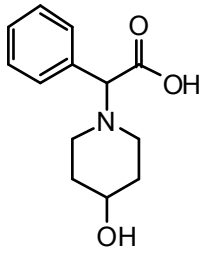
$[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; encontrado 325.20.

Se añadió una solución en metanol (10 ml) de cualquiera de los estereoisómeros de 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo (1.0 g, 3.1 mmol) a una suspensión de Pd al 10%/C (120 mg) en metanol (5.0 ml). La mezcla de reacción se expuso a un globo de hidrógeno con un control cuidadoso durante <50 min. Inmediatamente después de completarse la reacción, se filtró el catalizador a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío proporcionando Cap-7, contaminado con ácido fenilacético como una espuma color castaño (867.6 mg; la masa es superior al rendimiento teórico). El producto se usó en la etapa siguiente sin purificación adicional. RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (s ancho ap., 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); T_R = 0.31 (Condición II); índice de homogeneidad >90%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; encontrado 235.15; EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; encontrado 235.1440.

La síntesis de Cap-8 y Cap-9 se llevó a cabo de acuerdo con la síntesis de Cap-7 usando aminas apropiadas para la etapa de desplazamiento de SN_2 (es decir, 4-hidroxipiperidina para Cap-8 y (S)-3-fluoropirrolidina para Cap-9) y condiciones modificadas para la separación de los intermedios estereoisoméricos respectivos, como se describe

más adelante.

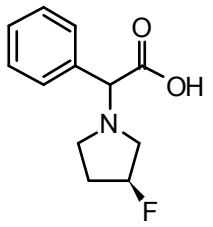
Cap-8



8a: enantiómero-1
8b: enantiómero-2

La separación estereoisomérica del intermedio 2-(4-hidroxipiperidin-1-il)-2-fenil acetato de bencilo se efectuó usando las siguientes condiciones: se disolvió el compuesto (500 mg) en etanol/heptano (5 ml/45 ml). La solución resultante se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 2 cm ID x 25 cm de longitud, 10 μm) eluyendo con 80:20 de heptano/etanol a 10 ml/min, controlada a 220 nm, proporcionando 186.3 mg de estereoisómero-1 y 209.1 mg de estereoisómero-2 como aceites viscosos amarillo claro. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de Cap-7 proporcionando Cap-8: RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 7.40 (d, J = 7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). T_R = 0.28 (Condición II); índice de homogeneidad >98%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; encontrado 236.07; EMAR: Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; encontrado 236.1283.

Cap-9

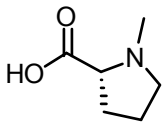


9a: diastereómero-1
9b: diastereómero-2

La separación diastereomérica del intermedio 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se efectuó usando las siguientes condiciones: se separó el éster (220 mg) en una columna HPLC quiral (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluyendo con 95% de CO_2 / 5% de metanol con 0.1% de TFA, a una presión de $10x10^5$ Pa, 70 ml/min de Caudal, y una temperatura de 35 °C. Se concentró el eluato de HPLC para los estereoisómeros respectivos y el residuo se disolvió en CH_2Cl_2 (20 ml) y se lavó con un medio acuoso (10 ml agua + 1 ml de solución saturada de $NaHCO_3$). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 92.5 mg de fracción-1 y 59.6 mg de fracción-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de Cap-7 para preparar Caps-9a y Cap-9b. Cap-9a (diastereómero-1; la muestra es una sal TFA como resultado de la purificación en una HPLC de fase inversa usando H_2O/metanol/TFA como disolvente): RMN de ^1H (DMSO-d_6, δ = 2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d de m, J = 53.7, 1H), 5.09 (s ancho, 1H), 3.84-2.82 (m ancho, 4H), 2.31-2.09 (m, 2H). T_R = 0.42 (Condición I); índice de homogeneidad >95%; CL-EM:

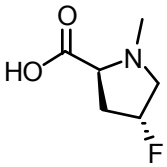
Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14; Cap-9b (diastereómero-2): RMN de ^1H (DMSO-d_6, δ = 2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d de m, J = 55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). T_R = 0.44 (Cond. I); CL-EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14.

Cap-10



A una solución de D-prolina (2.0 g, 17 mmol) y formaldehído (2.0 ml de 37% en peso en H_2O) en metanol (15 ml) se añadió una suspensión de Pd al 10%/C (500 mg) en metanol (5 ml). La mezcla se agitó bajo un globo de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío proporcionando Cap-10 como un sólido blanquecino (2.15 g). RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, J = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). T_R = 0.28 (Condición II); índice de homogeneidad >98%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; encontrado 129.96.

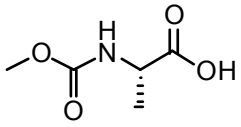
Cap-11



Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0.50 g, 3.8 mmol), formaldehído (0.5 ml de 37%

en peso en H_2O), HCl 12 N (0.25 ml) y Pd al 10%/C (50 mg) en metanol (20 ml) se agitó bajo un globo de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío. El residuo se recristalizó en isopropanol proporcionando la sal HCl de Cap-11 como un sólido blanco (337.7 mg). RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 5.39 (d m, J = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, J = 31.5, 13.5, 4.5, 1H), 3.33 (dd, J = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2,26 (m, 1H). T_R = 0.28 (Condición II); índice de homogeneidad >98%; CL-EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; encontrado 148.06.

Cap-12 (igual que Cap-52)

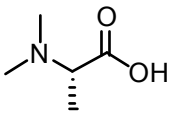


Ácido (S)-2-(metoxicarbonilamino)propanoico

Se disolvió L-alanina (2.0 g, 22.5 mmol) en solución acuosa al 10% de carbonato sódico (50 ml), y se añadió a la misma una solución en THF (50 ml) de cloroformiato de metilo (4.0 ml). La mezcla de reacción se agitó en condiciones ambientales durante 4.5 horas y se concentró a vacío. El sólido blanco resultante se disolvió en agua y se acidificó con HCl 1N hasta un pH ~ 2-3. Las soluciones resultantes se extrajeron con acetato de etilo (3 x 100 ml), y la fase orgánica reunida se secó (Na_2SO_4), se filtró y se concentró a vacío proporcionando un aceite

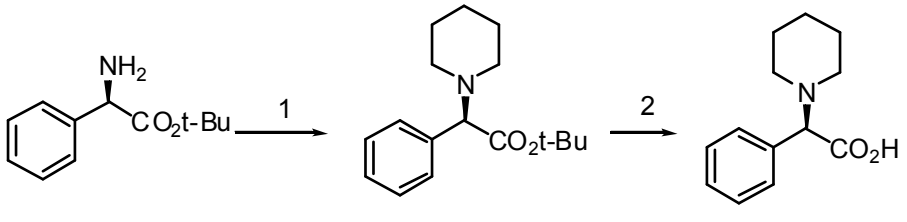
incoloro (2.58 g). Se purificaron 500 mg de este material por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando 150 mg de Cap-12 como un aceite incoloro. RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, J = 7.3, 0.8H), 7.10 (s ancho, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

Cap-13



Se agitó una mezcla de L-alanina (2.5 g, 28 mmol), formaldehído (8.4 g, 37% en peso), HCl 1N (30 ml) y Pd al 10%/C (500 mg) en metanol (30 ml) en una atmósfera de hidrógeno (344.64 kPa) durante 5 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (CELITE®) y el filtrado se concentró a vacío proporcionando la sal HCl de Cap-13 como un aceite que solidificó en reposo a vacío (4.4 g; la masa es superior al rendimiento teórico). El producto se usó sin purificación adicional. RMN de ^1H (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.1 (s ancho, 1H), 4.06 (q, J = 7.4, 1H), 2.76 (s, 6H), 1.46 (d, J = 7.3, 3H).

Cap-14



Cap-14

Ácido (R)-2-fenil-2-(piperidin-1-il)acético

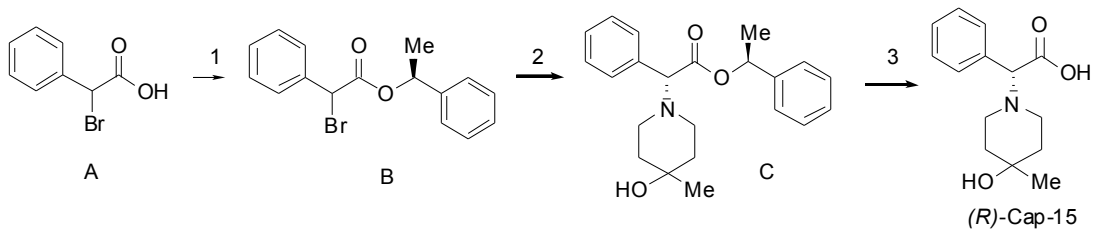
Etapa 1: Una mezcla éster *terc*-butílico de (R)-(-)-

D-fenilglicina (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) y ácido acético (0.352 ml, 6.15 mmol) se agitó en metanol a 0 °C. A esta mezcla se añadió dialdehído glutárico (2.23 ml, 12.3 mmol) gota a gota durante 5 minutos. La mezcla de reacción se agitó calentando hasta temperatura ambiente y se continuó agitando a la misma temperatura durante 16 horas. El disolvente se eliminó seguidamente y el residuo se repartió con NaOH acuoso al 10% y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta sequedad proporcionando un aceite transparente. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el éster intermedio (2.70 g, 56%) como un aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 10.9 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.59 (t, J = 11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J = 1.82 Hz, 3H), 1.40 (s, 9H). CL-EM: Anal. Calculado para $C_{17}H_{25}NO_2$: 275; encontrado: 276 $(M+H)^+$.

Etapa 2: A una solución agitada del éster intermedio (1.12 g, 2.88 mmol) en diclorometano (10 ml) se añadió TFA (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se concentró hasta sequedad dando un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere

C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%). Las fracciones apropiadas se reunieron y se concentraron hasta sequedad a vacío. El residuo se disolvió entonces en una cantidad mínima de metanol y se aplicó en cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se aclararon con metanol (40 ml) y luego eluyó el compuesto deseado usando amoníaco 2M en metanol (50 ml). Las fracciones que contenían producto se reunieron y concentraron y el residuo se suspendió en agua. La liofilización de esta solución proporcionó el compuesto del epígrafe (0.492 g, 78%) como un sólido amarillo claro. RMN de ^1H (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (s ancho, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (s ancho, 2H). CL-EM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

Cap-15



A B C *(R)*-Cap-15

Etapa 1: 2-Bromo-2-fenilacetato de (S)-1-feniletilo: A una mezcla de ácido α-bromofenilacético (10.75 g, 0.050 mol), (S)-(-)-1-feniletanol (7.94 g, 0.065 mol) y DMAP (0.61 g, 5.0 mmol) en diclorometano seco (100 ml) se añadió EDCI sólido (12.46 g, 0.065 mol) todo de una vez. La solución resultante se agitó a temperatura ambiente en Ar durante 18 horas y luego se diluyó con acetato de etilo, se

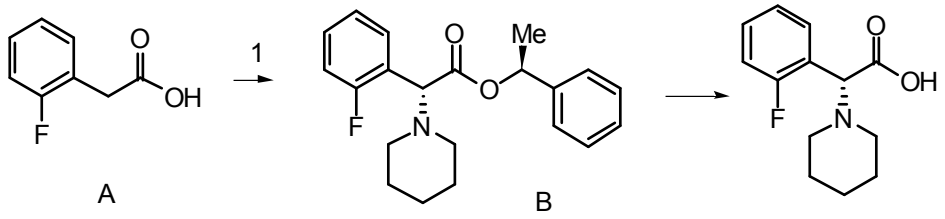
lavó (H_2O x 2, salmuera), se secó (Na_2SO_4), se filtró y se concentró dando un aceite amarillo pálido. La cromatografía ultrarrápida (SiO_2/ hexano-etilo acetato, 4:1) de este aceite proporcionó el compuesto del epígrafe (11.64 g, 73%) como un sólido blanco. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 1.5H), 1.51 (d, J = 6.6 Hz, 1.5H).

Etapa 2: (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo. A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (0.464 g, 1.45 mmol) en THF (8 ml) se añadió trietilamina (0.61 ml, 4.35 mmol), seguido por yoduro de tetrabutilamonio (0.215 g, 0.58 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-metil-4-hidroxipiperidina (0.251 g, 2.18 mmol) en THF (2 ml). La mezcla se agitó durante 1 hora a temperatura ambiente y luego se calentó a 55-60 °C (temperatura de baño de aceite) durante 4 horas. La mezcla de reacción enfriada se diluyó entonces con acetato de etilo (30 ml), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (0-60% de etilo acetato-hexano) proporcionando primero el isómero (S,R) del compuesto del epígrafe (0.306 g, 60%) como un sólido blanco y luego el correspondiente isómero (S,S)(0.120 g, 23%), también como un sólido blanco. Isómero (S,R): RMN de ^1H (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, J = 6.6

Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2,29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H). CL-EM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$. Isómero (S,S): RMN de ^1H (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, J = 6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, J = 6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H). CL-EM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$.

Etapa 3: ácido (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.185 g, 0.52 mmol) en diclorometano (3 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el compuesto del epígrafe (como sal TFA) como un sólido azulado pálido (0.128 g, 98%). CL-EM: Anal. Calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

Cap-16



(R)-Cap-16

Etapa 1: 2-(2-fluorofenil)acetato de (S)-1-feniletilo. Una mezcla de ácido 2-fluorofenilacético (5.45 g,

35.4 mmol), (S)-1-feniletanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) y DMAP (0.561 g, 4.60 mmol) en CH_2Cl_2 (100 ml) se agitó a temperatura ambiente durante 12 horas. El disolvente se concentró a continuación y el residuo se repartió con H_2O-acetato de etilo. Se separaron las fases y la fase acuosa se volvió a extraer con acetato de etilo (2x). Las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-20% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe como un aceite incoloro (8.38 g, 92%). RMN de ^1H (400 MHz, CD_3OD) δ 7.32 - 7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, J = 6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, J = 6.5 Hz, 3H).

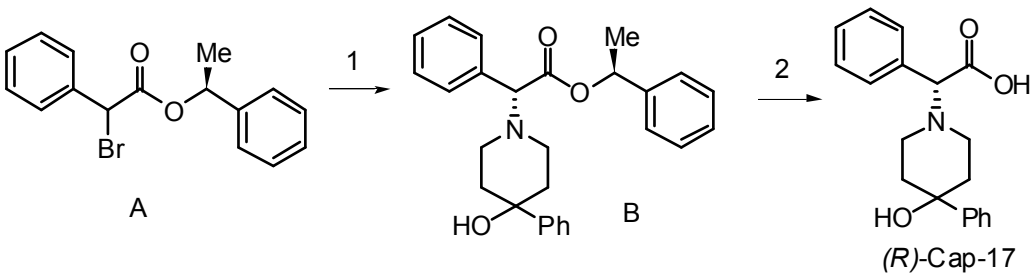
Etapa 2: 2-(2-Fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo). A una solución de 2-(2-fluorofenil)acetato de (S)-1-feniletilo (5.00 g, 19.4 mmol) en THF (1200 ml) a 0°C se añadió DBU (6.19 g, 40.7 mmol) y la solución se dejó calentar hasta temperatura ambiente mientras se agitaba durante 30 minutos. La solución se enfrió entonces hasta -78 °C y se añadió una solución de CBr_4 (13.5 g, 40.7 mmol) en THF (100 ml) y la mezcla se dejó calentar hasta -10 °C y se agitó a esta temperatura durante 2 horas. La mezcla de reacción se inactivó con NH_4Cl acuoso saturado y se separaron las fases. La fase acuosa se volvió a extraer con

acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. Al residuo se añadió piperidina (5.73 ml, 58.1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron entonces a vacío y el residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-30% de éter dietílico-hexano) proporcionando una mezcla pura de diastereoisómeros (relación 2:1 por RMN de ^1H) como un aceite amarillo (2.07 g, 31%), junto con material de partida sin reaccionar (2.53 g, 51%). Otra cromatografía de la mezcla diastereomérica (BIOTAGE®/ 0-10% éter dietílico-tolueno) proporcionó el compuesto del epígrafe como un aceite incoloro (0.737 g, 11%). RMN de ^1H (400 MHz, CD_3OD) δ 7.52 (ddd, J = 9.4, 7.6, 1.8 Hz, 1H), 7.33-7.40 (m, 1), 7.23-7.23 (m, 4H), 7.02-7.23 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 4.45 (s, 1H), 2.39-2.45 (m, 4H), 1.52 - 1.58 (m, 4H), 1.40-1.42 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H). CL-EM: Anal. Calculado para $C_{21}H_{24}FNO_2$: 341; encontrado: 342 $(M+H)^+$.

Etapa 3: ácido (R)-2-(2-fluorofenil)-2-(piperidin-1-il)acético: Una mezcla de 2-(2-fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo) (0.737 g, 2.16 mmol) y $Pd(OH)_2$ al 20%/C (0.070 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 2 horas. La solución se purgó entonces

con Ar, se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío. Esto proporcionó el compuesto del epígrafe como un sólido incoloro (0.503 g, 98%). RMN de ^{1}H (400 MHz, CD_3OD) δ 7.65 (ddd, J = 9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (s ancho, 4H), 1.62 (s ancho, 2H). CL-EM: Anal. Calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

Cap-17

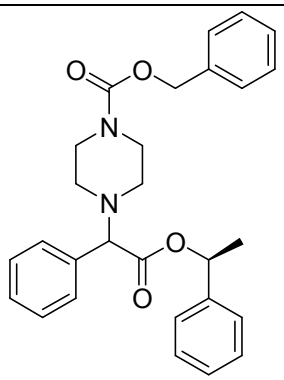


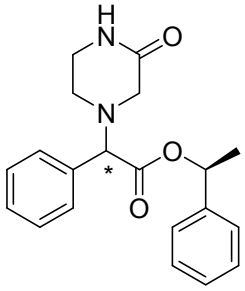
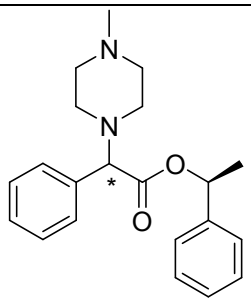
A B *(R)*-Cap-17

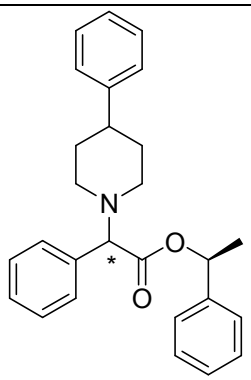
Etapa 1: (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo. A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1.50 g, 4.70 mmol) en THF (25 ml) se añadió trietilamina (1.31 ml, 9.42 mmol), seguido por yoduro de tetrabutilamonio (0.347 g, 0.94 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-fenil-4-hidroxipiperidina (1.00 g, 5.64 mmol) en THF (5 ml). La mezcla se agitó durante 16 horas y luego se diluyó con acetato de etilo (100 ml), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó en una columna de gel de sílice (acetato de etilo 0-60%-hexano) proporcionando una mezcla aproximadamente 2:1 de

diastereoisómeros, como se juzgó por RMN de ^{1}H. La separación de esos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (CHIRALCEL® OJ-H, 30 x 250mm; 20% etanol en CO_2 a 35 °C), dando primero el isómero (R) del compuesto del epígrafe (0.534 g, 27%) como un aceite amarillo y luego el isómero (S) correspondiente (0.271 g, 14%), también como un aceite amarillo. Isómero (S,R): RMN de ^{1}H (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, J = 11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, J = 11.1, 2.5 Hz, 1H), 2.20 (dt, J = 12.1, 4.6 Hz, 1H), 2.10 (dt, J = 12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, J = 6.5 Hz, 3H). CL-EM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$; Isómero (S,S): RMN de ^{1}H (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, J = 11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, J = 11.1, 2.5 Hz, 1H), 2.25 (dt, J = 12.1, 4.6 Hz, 1H), 2.12 (dt, J = 12.1, 4.6 Hz, 1H), 1.73 (dd, J = 13.6, 3.0 Hz, 1H), 1.64 (dd, J = 13.6, 3.0 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H). CL-EM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

Los ésteres siguientes se prepararon de una forma similar.

Intermedio-17a		Diastereómero 1: RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23 - 2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15 - 7.52 (m, 15H). CL-EM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.22; encontrado: 459.44 $(M+H)^+$. Diastereómero 2: RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27 - 2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19 - 7.27 (m, 3H) 7.27 - 7.44 (m, 10H). CL-EM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.22; encontrado: 459.44 $(M+H)^+$.

Intermedio -17b		Diastereómero 1: T_R = 11.76 min (Condición II); CL-EM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338.16 encontrado: 339.39 $(M+H)^+$; Diastereómero 2: T_R = 10.05 min (Condición II); CL-EM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338.16; encontrado: 339.39 $(M+H)^+$.
Intermedio -17c		Diastereómero 1: T_R = 4.55 min (Condición I); CL-EM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.20 Encontrado: 339.45 $(M+H)^+$; Diastereómero 2: T_R = 6.00 min (Condición I); CL-EM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.20 encontrado: 339.45 $(M+H)^+$.

Intermedio - 17d		Diastereómero 1: T_R = 7.19 min (Condición I); CL-EM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.22 encontrado: 400.48 $(M+H)^+$; Diastereómero 2: T_R = 9.76 min (Condición I); CL-EM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.22 encontrado: 400.48 $(M+H)^+$.

Condiciones de SFC quiral para determinar el tiempo de retención

Condición I

Columna: Columna CHIRALPAK® AD-H, 4.62X250 mm, 5µm

Disolventes: 90% de CO_2 - metanol al 10% con DEA al 0.1%

Temp: 35 °C

Presión: 15 MPa

Caudal: 2.0 ml/min.

UV controlado a 220 nm

Inyección: 1.0 mg/3 ml de metanol

Condición II

Columna: Columna CHIRALCEL® OD-H, 4.62X250 mm, 5µm

Disolventes: 90% de CO_2 - metanol al 10% con

DEA al 0.1%

Temp: 35 °C

Presión: 15 MPa

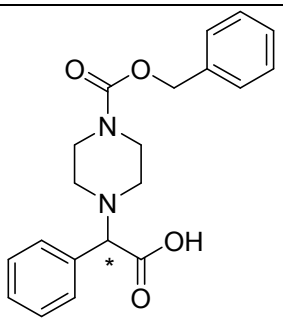
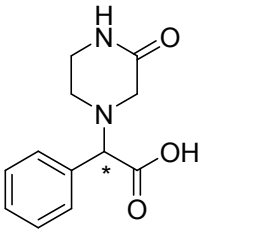
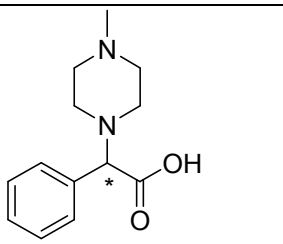
Caudal: 2.0 ml/min.

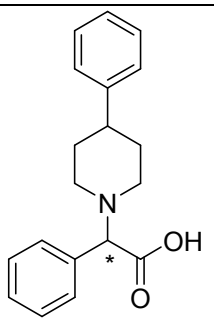
UV controlado a 220 nm

Inyección: 1.0 mg/ml de metanol

Cap-17, Etapa 2: ácido (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacético. A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.350 g, 0.84 mmol) en diclorometano (5 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando el compuesto del epígrafe (como sal TFA) como un sólido blanco (0.230 g, 88%). CL-EM: Anal. Calculado para $C_{19}H_{21}NO_3$: 311.15; encontrado: 312 $(M+H)^+$.

Los siguientes ácidos carboxílicos se prepararon en forma ópticamente pura de una forma similar:

Cap-17a		T_R = 2.21 (Condición II); RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 2.20 - 2.35 (m, 2H) 2.34 - 2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06 - 7.53 (m, 10H). CL-EM: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354.16; encontrado: 355.38 $(M+H)^+$.
Cap-17b		T_R = 0.27 (Condición III); CL-EM: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234.10; encontrado: 235.22 $(M+H)^+$.
Cap-17c		T_R = 0.48 (Condición II); CL-EM: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234.14; encontrado: 235.31 $(M+H)^+$.

Cap-17d		T_R = 2.21 (Condición I); CL-EM: Análisis calculado para: $C_{19}H_{21}NO_2$ 295.16; encontrado: 296.33 $(M+H)^+$.

Condiciones de CL-EM para determinar el tiempo de retención

Condición I

Columna: PHENOMENEX® Luna 4.6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Condición II

Columna: Waters-Sunfire 4.6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Condición III

Columna: PHENOMENEX® 10µ 3.0 X 50 mm

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

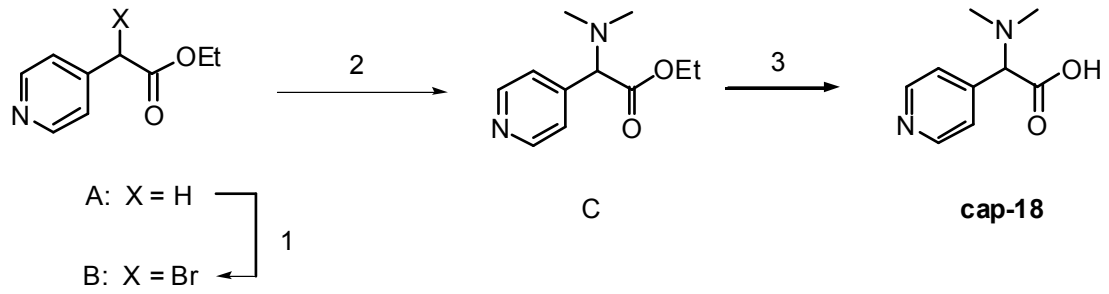
Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = metanol al 10% - H_2O al 90% - TFA al 0.1%

Disolvente B = metanol al 90% - H_2O al 10% - TFA al 0.1%

Cap-18



Etapa 1: 2-(4-piridil)-2-bromoacetato de (R,S)-etilo: A una solución de 4-piridilacetato de etilo (1.00 g, 6.05 mmol) en THF seco (150 ml) a 0 °C en argón se añadió DBU (0.99 ml, 6.66 mmol). La mezcla de reacción se dejó calentar

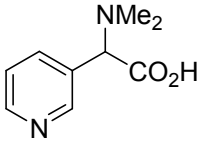
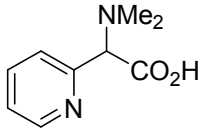
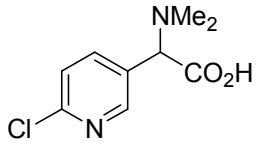
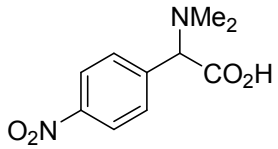
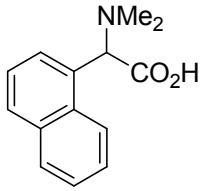
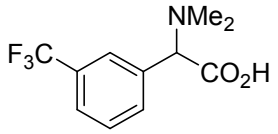
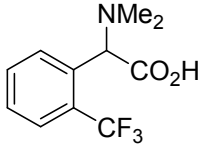
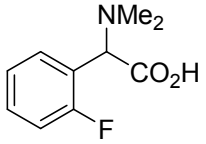
hasta temperatura ambiente durante 30 minutos y luego se enfrió hasta -78 °C. A esta mezcla se añadió CBr_4 (2.21 g, 6.66 mmol) y se continuó agitando a -78 °C durante 2 horas. Seguidamente la mezcla de reacción se inactivó con NH_4Cl acuoso saturado y se separaron las fases. La fase orgánica se lavó (salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El aceite amarillo resultante se purificó inmediatamente por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (1.40 g, 95%) como un aceite amarillo algo estable. RMN de ^1H (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.6, 1.8 Hz, 2H), 7.45 (dd, J = 4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). CL-EM: Anal. Calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243, 245 $(M+H)^+$.

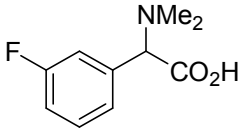
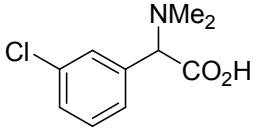
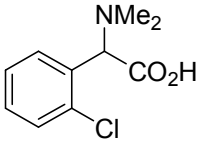
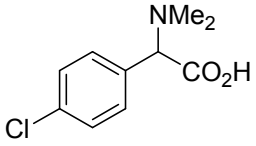
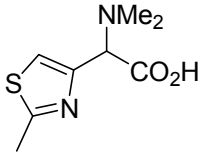
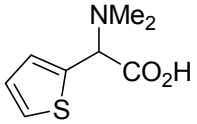
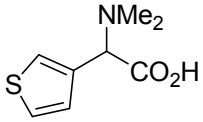
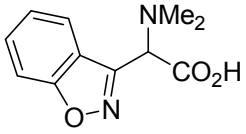
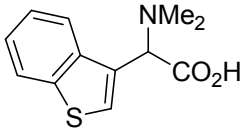
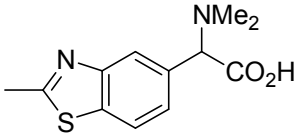
Etapa 2: 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1.40 g, 8.48 mmol) en DMF (10 ml) a temperatura ambiente se añadió dimetilamina (2M en THF, 8.5 ml, 17.0 mmol). Después de completarse la reacción (que se juzgó por cromatografía en capa fina) los volátiles se eliminaron a vacío y el residuo se purificó por cromatografía ultrarrápida (columna BIOTAGE®, 40+M SiO_2; 50%-100% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe (0.539 g,

31%) como un aceite amarillo claro. RMN de ^{1}H (400 MHz, $CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, J = 7.0 Hz). CL-EM: Anal. Calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

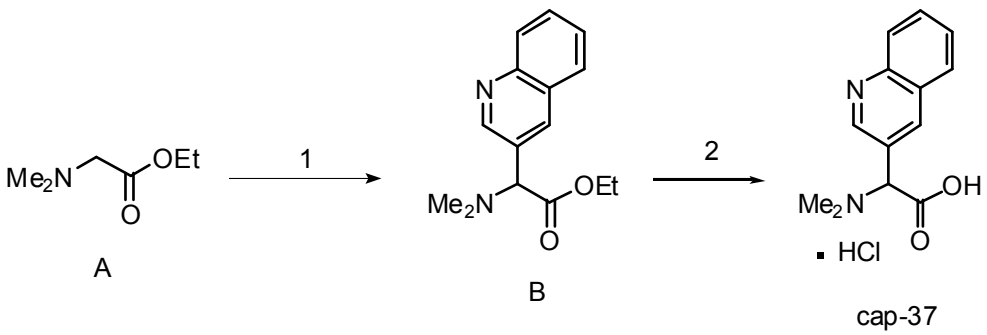
Etapa 3: ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.200 g, 0.960 mmol) en una mezcla de THF-metanol-H_2O (1:1:1, 6 ml) se añadió LiOH en polvo (0.120 g, 4.99 mmol) a temperatura ambiente. La solución se agitó durante 3 horas y luego se acidificó hasta pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de etilo y luego se liofilizó dando el diclorhidrato del compuesto del epígrafe como un sólido amarillo (que contenía LiCl). El producto se usó como tal en las posteriores etapas. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

Los siguientes ejemplos se prepararon de una forma similar usando el procedimiento descrito antes:

Cap-19		CL-EM: Anal. Calculado para $C_9H_{12}N_2O_2$: 180; encontrado: 181 $(M+H)^+$.
Cap-20		CL-EM: sin ionización. RMN de ^1H (400 MHz, CD_3OD) δ 8.55 (d, J = 4.3 Hz, 1H), 7.84 (t aparente, J = 5.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (t aparente, J = 5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		CL-EM: Anal. Calculado para $C_9H_{11Cl}N_2O_2$: 214, 216; encontrado: 215, 217 $(M+H)^+$.
Cap-22		CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-23		CL-EM: Anal. Calculado para $C_{14}H_{15}NO_2$: 229; encontrado: 230 $(M+H)^+$.
Cap-24		CL-EM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-25		CL-EM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-26		CL-EM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

Cap-27		CL-EM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 247; encontrado: 248 $(M+H)^+$.
Cap-28		CL-EM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-29		CL-EM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-30		CL-EM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.
Cap-31		CL-EM: Anal. Calculado para $C_8H_{12}N_2O_2S$: 200; encontrado: 201 $(M+H)^+$.
Cap-32		CL-EM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$.
Cap-33		CL-EM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$.
Cap-34		CL-EM: Anal. Calculado para $C_{11}H_{12}N_2O_3$: 220; encontrado: 221 $(M+H)^+$.
Cap-35		CL-EM: Anal. Calculado para $C_{12}H_{13}NO_2S$: 235; encontrado: 236 $(M+H)^+$.
Cap-36		CL-EM: Anal. Calculado para $C_{12}H_{14}N_2O_2S$: 250; encontrado: 251 $(M+H)^+$.

Cap-37



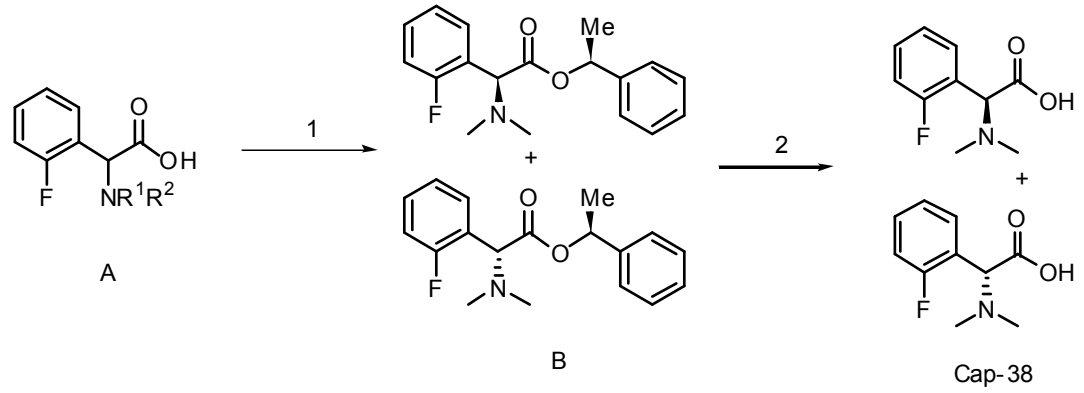
A B cap-37

Etapa 1: 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-etilo: Una mezcla de N,N-dimetilaminoacetato de etilo (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol), 3-bromoquinolina y tolueno (10 ml) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción se calentó entonces a 100 °C durante 12 horas, después de lo cual se enfrió hasta temperatura ambiente y se vertió en H_2O. La mezcla se extrajo con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó primero por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) y luego por cromatografía ultrarrápida (SiO_2/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (0.128 g, 17%) como un aceite naranja. RMN de ^1H (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H),

1.15 (t, J = 7.0 Hz, 3H). CL-EM: Anal. Calculado para $C_{15}H_{18}N_2O_2$: 258; encontrado: 259 $(M+H)^+$.

Etapa 2: Ácido (R,S) 2-(quinolin-3-il)-2-(N,N-dimetilamino)acético: Se calentó una mezcla de 2-(quinolin-3-il)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.122 g, 0.472 mmol) y HCl 6M (3 ml) a 100 °C durante 12 horas. El disolvente se eliminó a vacío proporcionando el diclorhidrato del compuesto del epígrafe (0.169 g, >100%) como una espuma amarillo claro. El material sin purificar se usó en las etapas siguientes sin purificación adicional. CL-EM: Anal. Calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

Cap-38



Etapa 1: 2-(Dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) y 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletil): A una mezcla de ácido (RS)-2-(dimetilamino)-2-(2-fluorofenil)acético (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) y (S)-1-feniletanol (2.09 g, 17.15 mmol) en CH_2Cl_2 (40 ml) se añadió EDCI (3.29 g, 17.15 mmol) y la mezcla se dejó agitando a temperatura

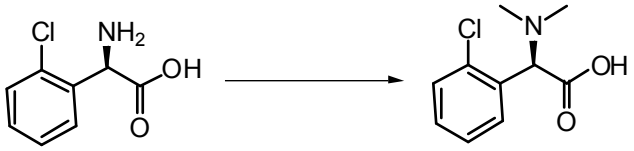
ambiente durante 12 horas. El disolvente se eliminó entonces a vacío y el residuo se repartió con acetato de etilo-H_2O. Se separaron las fases, la fase acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-50% de éter dietílico-hexano). La mezcla diastereomérica pura resultante se separó entonces por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-TFA al 0.1%) dando primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0.501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0.727 g. 18%), ambas como sus sales TFA. isómero (S,R): RMN de ^1H (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, J = 9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, J = 6.5 Hz, 3H). CL-EM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$; isómero (S,S): RMN de ^1H (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, J = 8.5, 1.5 Hz, 2H), 6.02 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, J = 6.5 Hz, 3H). CL-EM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$.

Etapa 2: Ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de 2-(dimetilamino)-2-(2-

fluorofenil)acetato de (R)-((S)-1-feniletilo), sal TFA (1.25 g, 3.01 mmol) y 20% de $Pd(OH)_2/C$ (0.125 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío. Esto dio el compuesto del epígrafe como un sólido incoloro (0.503 g, 98%). RMN de ^1H (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). CL-EM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

El isómero S se podía obtener a partir de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo), sal TFA de una forma similar.

Cap-39

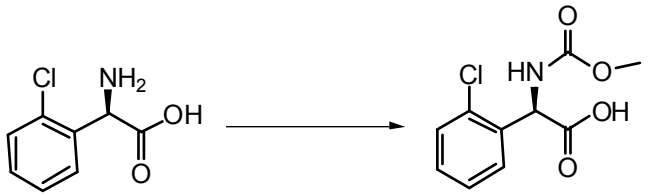


cap-39

Una mezcla de (R)-(2-clorofenil)glicina (0.300 g, 1.62 mmol), formaldehído (solución acuosa al 35%, 0.80 ml, 3.23 mmol) y 20% de $Pd(OH)_2/C$ (0.050 g) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de H_2) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío. El residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm;

CH_3CN-H_2O-TFA al 0.1%) dando la sal TFA del compuesto del epígrafe ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0.290 g, 55%). RMN de ^1H (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). CL-EM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

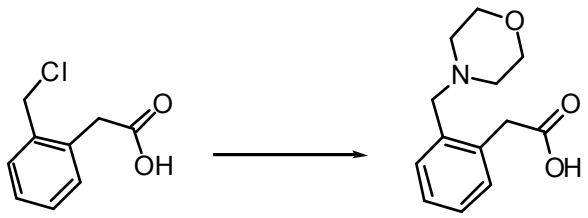
Cap-40



cap-40

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1.00 g, 5.38 mmol) y NaOH (0.862 g, 21.6 mmol) en H_2O (5.5 ml) se añadió cloroformiato de metilo (1.00 ml, 13.5 mmol) gota a gota. La mezcla se dejó agitando a 0 °C durante 1 hora y luego se acidificó mediante la adición de HCl concentrado (2.5 ml). La mezcla se extrajo con acetato de etilo (2x) y la fase orgánica reunida se lavó (H_2O, salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío dando el compuesto del epígrafe ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma amarillo-naranja (1.31 g, 96%). RMN de ^1H (400 MHz, CD_3OD) δ 7.39-7.43 (m, 2H), 7.29-7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). CL-EM: Anal. Calculado para $C_{10}H_{10}ClNO_4$: 243; encontrado: 244 $(M+H)^+$.

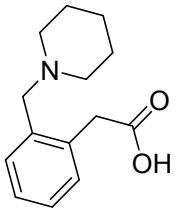
Cap-41

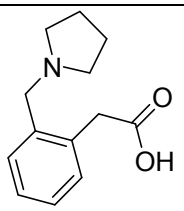
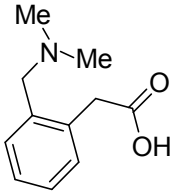
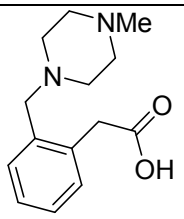


cap-41

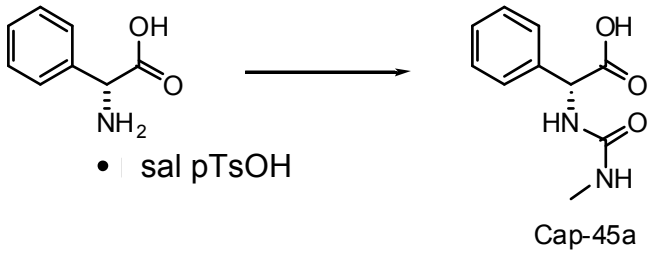
A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2.00 g, 10.8 mmol) en THF (20 ml) se añadió morfolina (1.89 g, 21.7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó entonces con acetato de etilo y se extrajo con H_2O (2x). La fase acuosa se liofilizó y el residuo se purificó por cromatografía sobre gel de sílice (BIOTAGE®/ 0-10% de metanol-CH_2Cl_2) dando el compuesto del epígrafe ácido 2-(2-(morfolinometil)fenil)acético como un sólido incoloro (2.22 g, 87%). RMN de ^1H (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (s ancho, 4H), 3.68 (s, 2H), 3.14 (s ancho, 4H). CL-EM: Anal. Calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

Los siguientes ejemplos se prepararon de igual modo usando el procedimiento descrito para Cap-41:

Cap-42		CL-EM: Anal. Calculado para $C_{14}H_{19}NO_2$: 233; encontrado: 234 $(M+H)^+$.

Cap-43		CL-EM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.
Cap-44		CL-EM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 194 $(M+H)^+$.
Cap-45		CL-EM: Anal. Calculado para $C_{14}H_{20}N_2O_2$: 248; encontrado: 249 $(M+H)^+$.

Cap-45a

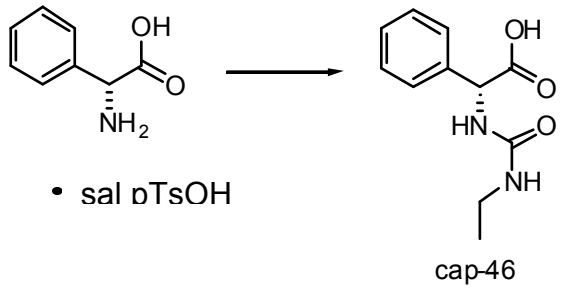


Cap-45a

Se añadió HMDS (1.85 ml, 8.77 mmol) a una suspensión de p-toluenosulfonato del ácido (R)-2-amino-2-fenilacético (2.83 g, 8.77 mmol) en CH_2Cl_2 (10 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió isocianato de metilo (0.5 g, 8.77 mmol) en una porción continuando la agitación durante 30 minutos. La reacción se inactivó mediante adición de H_2O (5 ml) y se filtró el precipitado resultante, se lavó con H_2O y n-hexanos, y se secó a vacío. Se recuperó ácido (R)-2-(3-metilureido)-2-

fenilacético (1.5 g; 82 %) como un sólido blanco y se usó sin purificación adicional. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.67 (s, 1H). CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_3$ 208.08 encontrado 209.121 $(M+H)^+$; HPLC PHENOMENEX® C-18 3.0 × 46 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, T_R = 1.38 min, índice de homogeneidad 90 %.

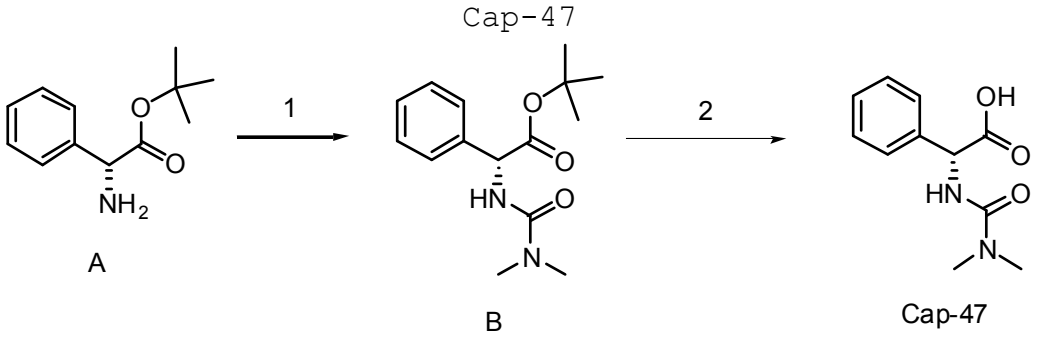
Cap-46



cap-46

El producto deseado se preparó de acuerdo con el procedimiento descrito para Cap-45a. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94 - 3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.68 (s, 1H). CL-EM: Anal. Calculado para $C_{11}H_{14}N_2O_3$ 222.10 encontrado 223.15 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 506 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 0.87 min, índice de

homogeneidad 90 %.

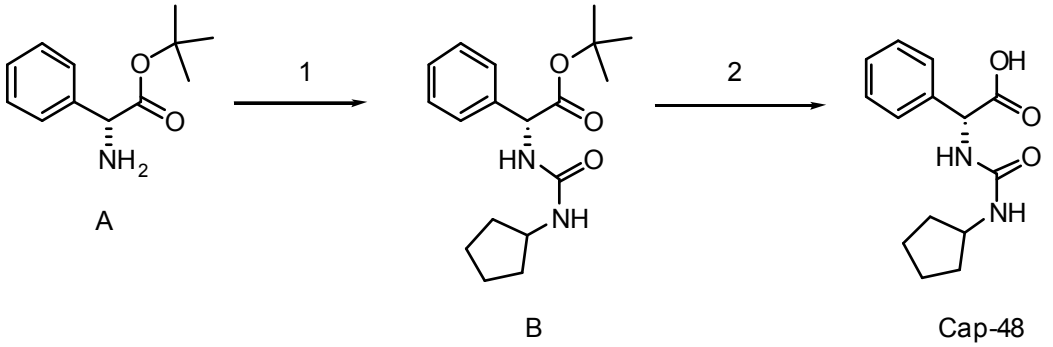


Etapa 1: 2-(3,3-Dimetilureido)-2-fenilacetato de (R)-*terc*-butilo: A una solución agitada de (R)-terc-butil-2-amino-2-fenilacetato (1.0 g, 4.10 mmol) y base de Hunig (1.79 ml, 10.25 mmol) en DMF (40 ml) se añadió cloruro de dimetilcarbamoílo (0.38 ml, 4.18 mmol) gota a gota durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se disolvió en acetato de etilo. La fase orgánica se lavó con H_2O, HCl ac. 1N y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3,3-dimetilureido)-2-fenilacetato de (R)-*terc*-butilo como un sólido blanco (0.86 g; 75%) y se usó sin purificación posterior. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, *J*=7.63 Hz, 1H) 6.55 (d, *J*=7.32 Hz, 1H) 7.24 - 7.41 (m, 5H). CL-EM: Anal. Calculado para $C_{15}H_{22}N_2O_3$ 278.16 encontrado 279.23 $(M+H)^+$; HPLC PHENOMENEX® LUNA C-18 4.6 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol,

0.1% de TFA, T_R = 2.26 min, índice de homogeneidad 97%.

Etapa 2: Ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-*terc*-butilo (0.86 g, 3.10 mmol) en CH_2Cl_2 (250 ml) se añadió TFA (15 ml) gota a gota y la solución resultante se agitó a ta durante 3 horas. El compuesto deseado precipitó entonces en solución con una mezcla de EtOAC:Hexanos (5:20), se separó por filtración y se secó a presión reducida. Se aisló ácido (R)-2-(3,3-dimetilureido)-2-fenilacético como un sólido blanco (0.59g, 86%) y se usó sin purificación posterior. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38 - 7.43 (m, 2H) 12.65 (s, 1H). CL-EM: Anal. Calculado para $C_{11}H_{14}N_2O_3$: 222.24; encontrado: 223.21 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 0.75 min, índice de homogeneidad 93%.

Cap-48



A B Cap-48

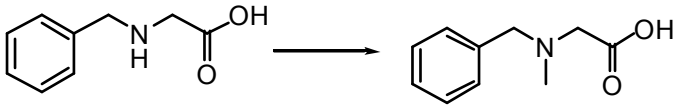
Etapa 1: 2-(3-Ciclopentilureido)-2-fenilacetato de

(R)-*terc*-butilo: A una solución agitada de clorhidrato del ácido (R)-2-amino-2-fenilacético (1.0 g, 4.10 mmol) y base de Hunig (1.0 ml, 6.15 mmol) en DMF (15 ml) se añadió isocianato de ciclopentilo (0.46 ml, 4.10 mmol) gota a gota y durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se suspendió en acetato de etilo. La fase orgánica se lavó con H_2O y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*terc*-butilo como un aceite opaco (1.32 g; 100 %) y se usó sin purificación posterior. RMN de ^1H (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). CL-EM: Anal. Calculado para $C_{18}H_{26}N_2O_3$ 318.19 encontrado 319.21 $(M+H)^+$; HPLC XTERRA® C-18 3.0 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, T_R = 2.82 min, índice de homogeneidad 96%.

Etapa 2: Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*terc*-butilo (1.31 g, 4.10 mmol) en CH_2Cl_2 (25 ml) se añadió TFA (4 ml) y trietilsilano (1.64 ml; 10.3 mmol) gota a gota, y la solución resultante se agitó a temperatura ambiente durante 6 horas.

Los componentes volátiles se eliminaron a presión reducida y el producto bruto se recristalizó en acetato de etilo/pentanos proporcionando ácido (R)-2-(3-ciclopentilureido)-2-fenilacético como un sólido blanco (0.69 g, 64%). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2H) 1.42 - 1.52 (m, 2H) 1.53 - 1.64 (m, 2H) 1.67 - 1.80 (m, 2H) 3.75 - 3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24 - 7.40 (m, 5H) 12.73 (s, 1H). CL-EM: Anal. Calculado para $C_{14}H_{18}N_2O_3$: 262.31; encontrado: 263.15 $(M+H)^+$. HPLC XTERRA® C-18 3.0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0.2% H_3PO_4, B = 10% de agua, 90% de metanol, 0.2% H_3PO_4, T_R = 1.24 min, índice de homogeneidad 100%.

Cap-49

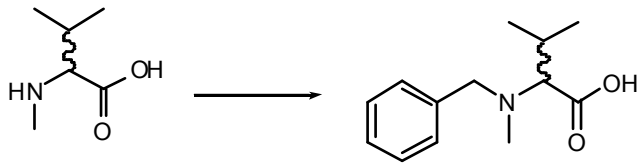


cap-49

A una solución agitada de ácido 2-(bencilamino)acético (2.0 g, 12.1 mmol) en ácido fórmico (91 ml) se añadió formaldehído (6.94 ml, 93.2 mmol). Después de cinco horas a 70 °C, la mezcla de reacción se concentró a presión reducida hasta 20 ml y precipitó un sólido blanco. Después de filtrar, las aguas madres se recogieron y se concentró además a presión reducida proporcionando el

producto bruto. La purificación por HPLC preparativa de fase inversa (XTERRA® 30 X 100 mm, detección a 220 nm, Caudal 35 ml/min, 0 a 35% de B durante 8 min; A = 90% de agua, 10 % de metanol, 0.1% de TFA, B = 10% de agua, 90 % de metanol, 0.1% de TFA) proporcionó el compuesto del epígrafe ácido 2-(bencil(metil)-amino)acético como su sal TFA (723 mg, 33%) como una cera incolora. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). CL-EM: Análisis calculado para: $C_{10}H_{13}NO_2$ 179.09; encontrado: 180.20 $(M+H)^+$.

Cap-50

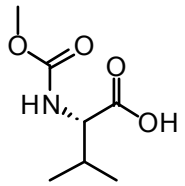


Cap-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico(0.50 g, 3.81 mmol) en agua (30 ml) se añadió K_2CO_3 (2.63 g, 19.1 mmol) y cloruro de bencilo (1.32 g, 11.4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se extrajo con acetato de etilo (30 ml x 2) y la fase acuosa se concentró a presión reducida proporcionando el producto bruto que se purificó por HPLC preparativa de fase inversa (XTERRA® 30 x 100mm, detección a 220 nm, Caudal 40 ml/min, 20 a 80% de B durante 6 min; A = 90% de agua, 10 % de metanol, 0.1% de TFA, B = 10% de agua, 90 % de metanol, 0.1% de TFA)

proporcionando ácido 2-(bencil(metil)amino)-3-metilbutanoico, sal TFA (126 mg, 19%) como una cera incolora. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33 - 2.48 (m, 1H) 2.54 - 2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29 - 7.65 (m, 5H). CL-EM: Análisis calculado para: $C_{13}H_{19}NO_2$ 221.14; encontrado: 222.28 $(M+H)^+$.

Cap-51

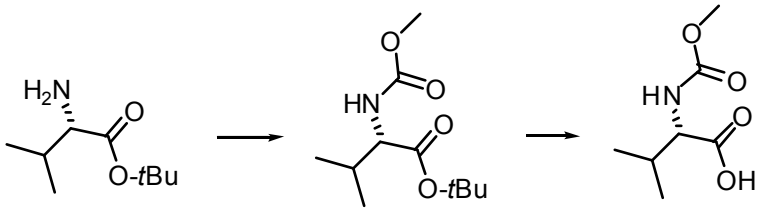


Ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico

Se añadió Na_2CO_3 (1.83g, 17.2 mmol) a una solución de NaOH (33 ml de 1M/H_2O, 33 mmol) de L-valina (3.9 g, 33.29 mmol) y la solución resultante se enfrió con baño de hielo-agua. Se añadió gota a gota durante 15 minutos cloroformiato de metilo (2.8 ml, 36.1 mmol), se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 3.25 horas. La mezcla de reacción se lavó con éter (50 ml, 3x), y la fase acuosa se enfrió con un baño de hielo-agua y se acidificó con HCl concentrado hasta un pH de 1-2, y se extrajo con CH_2Cl_2 (50 ml, 3x). La fase orgánica se secó ($MgSO_4$) y se evaporó a vacío proporcionando Cap-51 como un sólido blanco (6 g). RMN de ^{1}H para el rotámero dominante (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, J = 8.6, 1H), 3.84 (dd, J = 8.4, 6.0, 1H), 3.54 (s,

3H), 2.03 (m, 1H), 0.87 (m, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; encontrado 176.0922.

Cap-51 (ruta alternativa)



Ácido (S)-metoxicarbonilamino)-3-metilbutanoico

Se añadió DIEA (137.5 ml, 0.766 mol) a una suspensión de clorhidrato de 2-amino-3-metilbutanoato de (S)-*terc*-butilo (75.0 g, 0.357 mol) en THF (900 ml), y la mezcla se enfrió hasta 0 °C (baño de hielo/agua). Se añadió gota a gota durante 45 minutos cloroformiato de metilo (29.0 ml, 0.375 mol), se retiró el baño de enfriamiento y la mezcla heterogénea se agitó a temperatura ambiente durante 3 h. El disolvente se eliminó a presión reducida y el residuo se repartió entre EtOAc y agua (1 litro de cada uno). La fase orgánica se lavó con H_2O (1 l) y salmuera (1 l), se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El material bruto se hizo pasar a través de un lecho corto de gel de sílice (1 kg), eluyendo con hexanos (4 l) y EtOAc:hexanos 15:85 (4 l) proporcionando 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-*terc*-butilo como un aceite transparente (82.0 g, 99% de rendimiento). RMN de ^1H (500 MHz, DMSO-d_6, δ = 2.5 ppm) 7.34 (d, J = 8.6, 1 H), 3.77 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.05 (m,

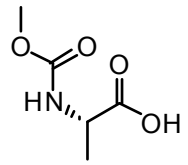
1 H), 1.39 (s, 9 H), 0.83 - 0.92 (m, 6 H). RMN de ^{13}C (126 MHz, DMSO-d_6, δ = 39.2 ppm) 170.92, 156.84, 80.38, 60.00, 51.34, 29.76, 27.62, 18.92, 17.95. CL-EM: $[M+Na]^+$ 254.17.

Se añadieron ácido trifluoroacético (343 ml, 4.62 mol) y Et_3SiH (142 ml, 0.887 mol) secuencialmente a una solución de 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-*terc*-butilo (82.0 g, 0.355 mol) en CH_2Cl_2 (675 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. El componente volátil se eliminó a presión reducida y el aceite resultante se trituró con éter de petróleo (600 ml) proporcionando un sólido blanco, que se filtró y se lavó con hexanos (500 ml) y éter de petróleo (500 ml). La recristalización en EtOAc/éter de petróleo proporcionó Cap-51 como cristales a modo de escamas blancos (54.8 g, 88 % de rendimiento). PF = 108.5-109.5 °C. RMN de ^1H (500 MHz, DMSO-d_6, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, J = 8.6, 1 H), 3.83 (dd, J = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, J = 8.9, 7.0, 6 H). RMN de ^{13}C (126 MHz, DMSO-d_6, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98. CL-EM: $[M+H]^+$ = 176.11. Análisis calculado para $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Encontrado: C, 48.17; H, 7.55; N, 7.99. Rotación óptica: $[\alpha]_D$ = -4.16 (12.02 mg/ml; MeOH). Pureza óptica: >99.5 % ee. Nota: la valoración de la pureza óptica se realizó en el derivado éster metílico de Cap-51, que se preparó según un protocolo de esterificación

normalizado en $TMSCHN_2$ (benceno/MeOH). Condiciones del análisis de HPLC: columna, CHIRALPAK® AD-H (4.6 x 250mm, 5μm); disolvente, heptano al 95% / IPA al 5% (isocrático); caudal, 1 ml/min; temperatura, 35 °C; UV controlado a 205 nm.

[Nota: Cap-51 también se podía adquirir de Flamm.]

Cap-52 (Igual que Cap-12)

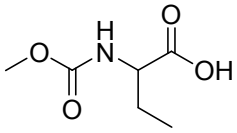


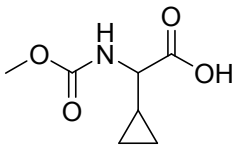
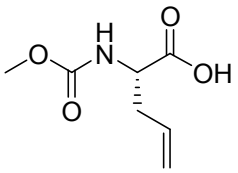
Ácido (S)-2-(metoxicarbonilamino)propanoico

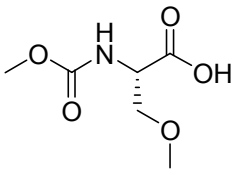
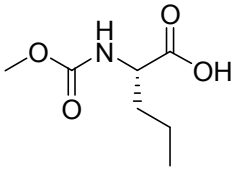
Cap-52 se sintetizó a partir de L-alanina de acuerdo con el procedimiento descrito para la síntesis de Cap-51. Con fines caracterizadores, se purificó una porción del material bruto por una HPLC de fase inversa (H_2O/metanol/TFA) proporcionando Cap-52 como un aceite incoloro viscoso. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.49 (s ancho, 1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (s ancho aparente, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

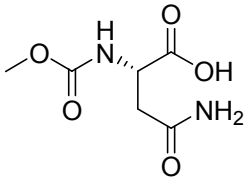
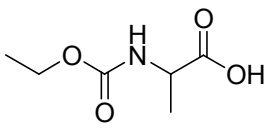
Cap-53 a Cap-64

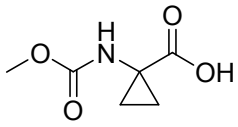
Se prepararon Cap-53 a Cap-64 a partir de materiales partida apropiados de acuerdo con el procedimiento descrito para la síntesis de Cap-51, con las modificaciones indicadas si las hubiera.

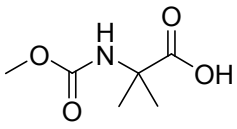
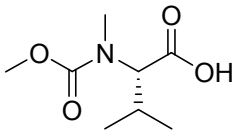
Cap	Estructura	Datos
Cap-53a: (R) Cap-53b: (S) (ácido (S)-2-(metoxicarbonilamino)-butanoico)		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (s ancho, 1H), 7.4 (d, J = 7.9, 0.9H), 7.06 (s ap., 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, J = 7.3, 3H). T_R = 0.77 minutos (Cond. II); CL-EM: Anal. Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; encontrado 184.07. EMAR Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; encontrado 184.0592.

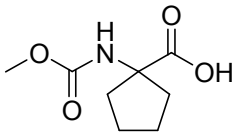
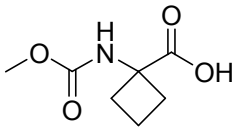
Cap	Estructura	Datos
Cap-54a: (R) Cap-54b: (S) (ácido (S)-2-ciclopropil-2-(metoxicarbonilamino) acético)		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, J = 7.6, 0.9H), 7.25 (s ap., 0.1H), 3.52 (s, 3H), 3.36-3,33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). EMAR Calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; encontrado 174.0771
Cap-55		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, J = 8.2, 0.9H), 7.07 (s ap., 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, J = 17.1, 1H), 5.04 (d, J = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2,29 (m, 1H).

Cap	Estructura	Datos
Cap-56 ácido (S)-3-metoxi-2-(metoxicarbonila-mino)-propanoico		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, J = 8.3, 0.9H), 6.96 (s ap., 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).
Cap-57		RMN de 1H (DMSO-d6, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, J = 7.7, 0.08H), 7.40 (d, J = 7.9, 0.76H), 7.19 (d, J = 8.2, 0.07H), 7.07 (d, J = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1,26 (m, 2H), 0.85 (t, J = 7.4, 3H). CL (Cond. II): TR = 1.39 CL-EM: Anal. Calculado para [M+H]+ C7H14NO4 : 176.09; encontrado 176.06.

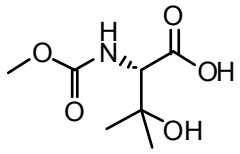
Cap	Estructura	Datos
Cap-58		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (s ancho, 1H), 7.35 (s,1H), 7.31 (d, J = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, J = 15.5, 5.4, 1H), 2.43 (dd, J = 15.6, 8.0, 1H). T_R = 0.16 min (Cond. II); CL-EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; encontrado 191.14.
Cap-59a: (R) Cap-59b: (S)		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.49 (s ancho, 1H), 7.40 (d, J = 7.3, 0.89H), 7.04 (s ancho, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, J = 7.3, 3H), 1.15 (t, J = 7.2, 3H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; encontrado 162.0771.

Cap	Estructura	Datos
Cap-60		El material bruto se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando un aceite viscoso incoloro que cristalizó en un sólido blanco al exponerse a alto vacío. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.38 (s ancho, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (dos s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; encontrado 160.0604.

Cap	Estructura	Datos
Cap-61		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.27 (s ancho, 1H), 7.40 (s ancho, 1H), 3.50 (s, 3H), 1.32 (s, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; encontrado 162.0765.
Cap-62		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.74 (s ancho, 1H), 4.21 (d, J = 10.3, 0.6H), 4.05 (d, J = 10.0, 0.4H), 3.62/3.60 (dos singletes, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, J = 6.3, 3H), 0.81 (d, J = 6.6, 3H). CL-EM: Anal. Calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; encontrado 188.05.

Cap	Estructura	Datos
Cap-63		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21 (s ancho, 1H), 7.42 (s ancho, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; encontrado 188.19.
Cap-64		[Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (s ancho, 1H), 7.77 (s, 0.82H), 7.56/7.52 (s ancho solapante, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

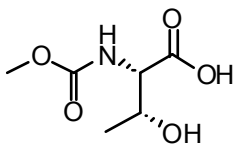
Cap-65



Se añadió cloroformiato de metilo (0.65 ml, 8.39 mmol) gota a gota durante 5 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 ml de 1M/H_2O, 8.2 mmol) y ácido (S)-2-amino-3-hidroxi-3-metilbutanoico (1.04 g, 7.81 mmol). La mezcla de reacción se agitó durante 45 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 3.75 horas. La mezcla de reacción se lavó con CH_2Cl_2, y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 1-2. El componente volátil se eliminó a vacío y el residuo se suspendió en una mezcla 2:1 de MeOH/CH_2Cl_2 (15 ml) y se filtró, y el filtrado se sometió a evaporación rotativa proporcionando Cap-65 como una espuma semiviscosa blanca (1.236 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 6.94 (d, J = 8.5, 0.9 H), 6.53 (s ancho, 0.1H), 3.89 (d, J = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

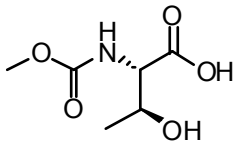
Cap-66 y Cap-67 se prepararon a partir de materiales de partida disponibles comercialmente usando el procedimiento descrito para la síntesis de Cap-65.

Cap-66



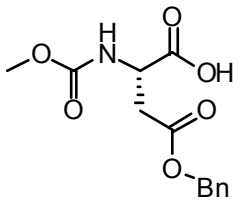
RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (s ancho, 1H), 7.07 (d, J = 8.3, 0.13H), 6.81 (d, J = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, J = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, J = 6.2, 3H). [Nota: solo se indican las señales dominantes de NH].

Cap-67



RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (s ancho, 1H), 7.25 (d, J = 8.4, 0.75H), 7.12 (d ancho, J = 0.4, 0.05H), 6.86 (s ancho, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, J = 6.3, 3H). [Nota: solo se indican las señales dominantes de NH].

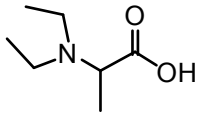
Cap-68



Se añadió cloroformiato de metilo (0.38 ml, 4.9 mmol) gota a gota a una mezcla de NaOH 1N (ac) (9.0 ml, 9.0 mmol), $NaHCO_3$ 1M (ac) (9.0 ml, 9.0 mol), éster β-bencílico del ácido L-aspártico (1.0 g, 4.5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó en condiciones ambientales

durante 3 horas, y luego se lavó con acetato de etilo (50 ml, 3x). La fase acuosa se acidificó con HCl 12N hasta un pH ~ 1-2, y se extrajo con acetato de etilo (3 x 50 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron a vacío proporcionando Cap-68 como un aceite amarillo claro (1.37g; la masa es superior al rendimiento teórico, y el producto se usó sin purificación adicional). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (s ancho, 1H), 7.55 (d, J = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, J = 12.8, 1H), 5.10 (d, J = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, J = 16.2, 5.5, 1H), 2.71 (dd, J =16.2, 8.3, 1H). CL (Cond. II): T_R = 1.90 min; CL-EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; encontrado 282.12.

Cap-69a y Cap-69b



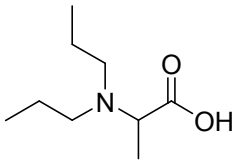
Cap-69a: enantiómero (R)
Cap-69b: enantiómero (S)

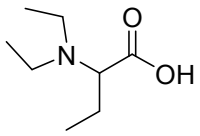
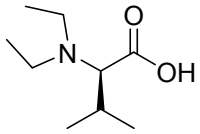
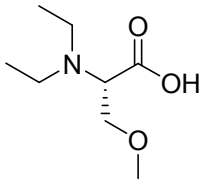
Se añadió $NaCNBH_3$ (2.416 g, 36.5 mmol) en lotes a una solución acuosa enfriada (~15°C) (17 ml)/MeOH (10 ml) de alanina (1.338 g, 15.0 mmol). Unos pocos minutos después se añadió gota a gota durante 4 minutos acetaldehído (4.0 ml, 71.3 mmol), se retiró entonces el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 6 horas. Se añadió más acetaldehído (4.0 ml) y la reacción se agitó durante 2 horas. Se añadió HCl concentrado

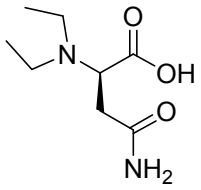
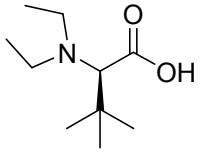
lentamente a la mezcla de reacción hasta que el pH alcanzó ~ 1.5, y la mezcla resultante se calentó durante 1 hora a 40°C. La mayoría del componente volátil se eliminó a vacío y el residuo se purificó con una resina de intercambio iónico DOWEX® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado mezclando 18 ml de NH_4OH y 282 ml de agua) proporcionando Cap-69 (2.0 g) como un sólido higroscópico blando blanquecino. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, J = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, J = 7.1, 3H), 1.13 (t, J = 7.3, 6H).

Cap-70 a Cap-74x

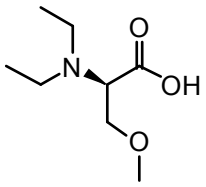
Cap-70 a Cap-74x se prepararon de acuerdo con el procedimiento descrito para la síntesis de Cap-69 usando materiales de partida apropiados.

Cap-70a: (R) Cap-70b: (S)		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, J = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, J = 7.3, 3H), 0.85 (t, J = 7.5, 6H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.13.

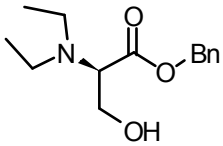
Cap-71a: (R) Cap-71b: (S)		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, J = 7.2, 6H), 0.91 (t, J = 7.3, 3H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; encontrado 160.06.
Cap-72		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, J = 7.1, 6H), 0.91 (d, J = 6.5, 3H), 0.85 (d, J = 6.5, 3H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.15.
Cap-73		RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (s ancho, 1H), 3.77 (dd, J = 10.8, 4.1.1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, J = 7.2, 6H).

Cap-74		RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, J = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, J = 15.6, 7.0, 1H), 2.36 (dd, J = 15.4, 6.3, 1H), 1.09 (t, J = 7.2, 6H). T_R = 0.125 minutos (Cond. II); CL-EM: Anal. Calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.13.
Cap-74x		CL-EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; encontrado 188.21

Cap-75



Cap-75, etapa a



Se añadió $NaBH_3CN$ (1.6 g, 25.5 mmol) a una solución enfriada (baño de hielo/agua) en agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Se añadió acetaldehído (1.5 ml, 12.5 mmol) gota a gota durante 5 min, se retiró el baño de enfriamiento, y la mezcla de reacción se agitó en

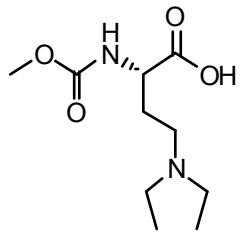
condiciones ambientales durante 2 horas. La reacción se inactivó cuidadosamente con HCl 12N y se concentró a vacío. El residuo se disolvió en agua y se purificó con una HPLC de fase inversa ($MeOH/H_2O$/TFA) proporcionando la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite incoloro viscoso (1.9 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.73 (s ancho, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). CL-EM (Cond. II): T_R = 1.38 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; encontrado 252.19.

Cap-75

Se añadió NaH (0.0727 g, 1.82 mmol, 60%) a una solución enfriada (hielo-agua) en THF (3.0 ml) de la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0.3019 g, 0.8264 mmol) preparada antes, y la mezcla se agitó durante 15 min. Se añadió yoduro de metilo (56 µl, 0.90 mmol) y se continuó agitando durante 18 horas dejando que el baño se descongelara hasta condiciones ambiente. La reacción se inactivó con agua y se cargó en un cartucho MCX preacondicionado con MeOH (6 g) y se lavó con metanol seguido por elución del compuesto con NH_3 2N/Metanol. La eliminación del componente volátil a vacío proporcionó Cap-75, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semisólido amarillo (100 mg). El

producto se usó como tal sin purificación adicional.

Cap-76

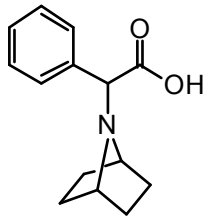


Se añadió $NaCNBH_3$ (1.60 g, 24.2 mmol) en cargas a una solución enfriada (~15 °C) en agua/MeOH (12 ml cada uno) de ácido (S)-4-amino-2-(*terc*-butoxicarbonilamino) butanoico (2.17 g, 9.94 mmol). Unos pocos minutos después se añadió acetaldehído (2.7 ml, 48.1 mmol) gota a gota durante 2 min, se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 3.5 horas. Se añadió más acetaldehído (2.7 ml, 48.1 mmol) y la reacción se agitó durante 20.5 horas. Se eliminó a vacío la mayoría del componente MeOH, y la mezcla restante se trató con HCl concentrado hasta que su pH llegó a ~ 1.0 y luego se calentó durante 2 horas a 40 °C. El componente volátil se eliminó a vacío, y el residuo se trató con HCl 4 M/dioxano (20 ml) y se agitó en condiciones ambientales durante 7.5 horas. El componente volátil se eliminó a vacío y el residuo se purificó con resina de intercambio iónico DOWEX® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado a partir de 18 ml de NH_4OH y 282 ml de agua) proporcionando el intermedio ácido (S)-2-amino-4-

(dietilamino)butanoico como un sólido blanquecino (1.73 g).

Se añadió cloroformiato de metilo (0.36 ml, 4.65 mmol) gota a gota durante 11 min a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 ml de 1M/H_2O, 4.6 mmol) y el producto anterior (802.4 mg). La mezcla de reacción se agitó durante 55 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 5.25 horas. La mezcla de reacción se diluyó con un volumen igual de agua y se lavó con CH_2Cl_2 (30 ml, 2x), y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta un pH en torno a 2. El componente volátil se eliminó a vacío y el material bruto se desbasificó con resina MCX (6.0g; la columna se lavó con agua, y la muestra se eluyó con NH_3 2.0 M/MeOH) proporcionando Cap-76 impuro como un sólido blanquecino (704 mg). RMN de ^1H (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, J = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J = 7.3, 6H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; encontrado 233.24.

Cap-77a y Cap-77b

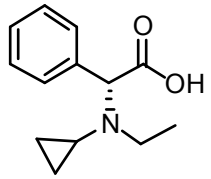


Cap-77a: enantiómero-1
Cap-77b: enantiómero-2

La síntesis de Cap-77 se llevó a cabo de acuerdo con el procedimiento descrito para Cap-7 usando 7-

azabiciclo[2.2.1]heptano para la etapa de desplazamiento SN_2, y efectuando la separación estereoisomérica del intermedio 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando las siguientes condiciones: el intermedio (303.7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna HPLC quiral (columna Chiracel AD-H, 30 x 250 mm, 5 um) eluyendo con 90% de CO_2-10% de EtOH a 70 ml/min, y una temperatura de 35 °C proporcionando 124.5 mg de estereoisómero-1 y 133.8 mg de estereoisómero-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de Cap-7 proporcionando Cap-77: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (s ancho aparente, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). CL (Cond. I): T_R = 0.67 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; encontrado 232.18. EMAR: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; encontrado 232.1340.

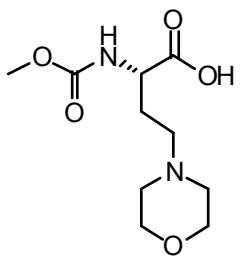
Cap-78



Se añadió $NaCNBH_3$ (0.5828 g, 9.27 mmol) a una mezcla de la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético (un intermedio en la síntesis de Cap-3; 0.9923 mg, 4.60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1.640

g, 9.40 mmol) en MeOH (10 ml), y se calentó la mezcla semiheterogénea a 50 °C con un baño de aceite durante 20 horas. Se añadieron más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0.86 mmol) y $NaCNBH_3$ (52 mg, 0.827 mmol) y la mezcla de reacción se calentó otras 3.5 horas. Se dejó enfriar hasta temperatura ambiente y se acidificó ~ pH entorno a 2 con HCl concentrado, y la mezcla se filtró y el filtrado se evaporó en un evaporador rotatorio. El material bruto resultante se suspendió en i-PrOH (6 ml) y se calentó para efectuar la disolución y la parte no disuelta se separó por filtración y el filtrado se concentró a vacío. Se purificó aproximadamente 1/3 del material bruto resultante con una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando la sal TFA de Cap-78 como un aceite incoloro viscoso (353 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz; después de intercambio de D_2O): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (s ancho aparente, 1H), 2.66 (m, 1H), 1.26 (t, J = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). CL (Cond. I): T_R = 0.64 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; encontrado 220.21. EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; encontrado 220.1343.

Cap-79



Se burbujeó ozono a través de una solución enfriada

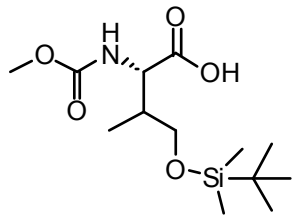
(-78 °C) en CH_2Cl_2 (5.0 ml) de Cap-55 (369 mg, 2.13 mmol) durante aproximadamente 50 min hasta que la mezcla de reacción alcanzó un tinte de color azul. Se añadió Me_2S (10 gotas de pipeta) y la mezcla de reacción se agitó durante 35 min. Se reemplazó el baño de -78 °C con un baño a -10 °C y se continuó agitando durante otros 30 min, y luego se eliminó el componente volátil a vacío proporcionando un aceite viscoso incoloro.

Se añadió $NaBH_3CN$ (149 mg, 2.25 mmol) a una solución en MeOH (5.0 ml) del material bruto anterior y morfolina (500 µl, 5.72 mmol) y la mezcla se agitó en condiciones ambientales durante 4 horas. Se enfrió hasta temperatura de hielo-agua y se trató con HCl concentrado para llevar el pH a ~2.0, y luego se agitó durante 2.5 horas. El componente volátil se eliminó a vacío, y el residuo se purificó con una combinación de resina MCX (lavado con MeOH; elución con NH_3 2.0 N/MeOH) y una HPLC de fase inversa (H_2O/MeOH/TFA) proporcionando Cap-79 que contenía una cantidad desconocida de morfolina.

Con el fin de consumir la morfolina contaminante, se disolvió el material anterior en CH_2Cl_2 (1.5 ml) y se trató con Et_3N (0.27 ml, 1.94 mmol) seguido por anhídrido acético (0.10 ml, 1.06 mmol) y se agitó en condiciones ambientales durante 18 horas. Se añadieron THF (1.0 ml) y H_2O (0.5 ml) y se continuó agitando durante 1.5 horas. El componente volátil

se eliminó a vacío, y el residuo resultante se hizo pasar a través de resina MCX (lavado con MeOH; elución con NH_3 2.0 N/MeOH) proporcionando Cap-79 impuro como un aceite viscoso marrón, que se usó para la etapa siguiente sin purificación adicional.

Cap-80a y Cap-80b



Cap-80a: diastereómero S/S
Cap-80b: diastereómero S/R

Se añadió $SOCl_2$ (6.60 ml, 90.5 mmol) gota a gota durante 15 min a una mezcla enfriada (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10.04g, 44.98 mmol) y MeOH (300 ml), se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 29 horas. Se eliminó la mayor parte del componente volátil a vacío y el residuo se repartió cuidadosamente entre EtOAc (150 ml) y solución saturada de $NaHCO_3$. La fase acuosa se extrajo con EtOAc (150 ml, 2x), y la fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 4-metil-2-aminosuccinato de (S)-1-bencilo como un aceite incoloro (9.706g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (t aparente, J = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). CL (Cond. I): T_R = 0.90 min; CL-EM: Anal. Calculado para $[M+H]^+$

$C_{12}H_{16}NO_4$: 238.11; encontrado 238.22.

Se añadió $Pb(NO_3)_2$ (6.06 g, 18.3 mmol) durante 1 minuto a una solución en CH_2Cl_2 (80 ml) de 4-metil-2-aminosuccinato de (S)-1-bencilo (4.50 g, 19.0 mmol), 9-bromo-9-fenil-9H-fluoreno (6.44 g, 20.0 mmol) y Et_3N (3.0 ml, 21.5 mmol) y la mezcla heterogénea se agitó en condiciones ambientales durante 48 horas. La mezcla se filtró y el filtrado se trató con $MgSO_4$ y se filtró de nuevo y el filtrado final se concentró. El material bruto resultante se sometió a una purificación en BIOTAGE® (350 g gel de sílice, elución con CH_2Cl_2) proporcionando 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo como aceite incoloro muy viscoso (7.93 g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J = 12.4, 1H), 4.51 (d, J = 12.6, 1H), 3.78 (d, J = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, parcialmente solapado con disolvente). CL (Cond. I): T_R = 2.16 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; encontrado 478.19.

Se añadió LiHMDS (9.2 ml de 1.0 M/THF, 9.2 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) THF (50 ml) de 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo (3.907 g, 8.18 mmol) y se agitó durante ~1 horas. Se añadió MeI (0.57 ml, 9.2 mmol) gota a gota durante 8 min a la mezcla y se continuó agitando

durante 16.5 horas dejando que el baño de enfriamiento se descongelara hasta temperatura ambiente. Después de inactivar con solución saturada de NH_4Cl (5 ml), se eliminó a vacío la mayor parte del componente orgánico y el residuo se repartió entre CH_2Cl_2 (100 ml) y agua (40 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se purificó con un BIOTAGE® (350 g gel de sílice; 25% de EtOAc/hexanos) proporcionando 3.65 g de una mezcla de diastereoisómeros 2S/3S y 2S/3R de 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de 1-bencilo en una relación ~1.0:0.65 (RMN de ^1H). La estereoquímica del isómero dominante no se determinó en este paso y la mezcla se sometió a la etapa siguiente sin separación. Datos parciales de RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): Diastereómero mayoritario, δ 4.39 (d, J = 12.3, 1H de CH_2), 3.33 (s, 3H, solapado con señal de H_2O), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); Diastereómero minoritario, δ 4.27 (d, J =12.3, 1H de CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). CL (Cond. I): T_R = 2.19 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; encontrado 492.15.

Se añadió hidruro de diisobutilaluminio (20.57 ml de 1.0 M en hexanos, 20.57 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) en THF (120 ml) de 4-metil-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (2S)-1-bencilo (3.37 g, 6.86 mmol) preparado antes y se agitó a -78

°C durante 20 horas. La mezcla de reacción se separó del baño de enfriamiento y se vertió rápidamente en H_3PO_4 ~1M/H_2O (250 ml) con agitación y la mezcla se extrajo con éter (100 ml, 2x). La fase orgánica reunida se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. Se preparó una malla de gel de sílice del material bruto y se sometió a cromatografía (25% de EtOAc/hexanos; elución por gravedad) proporcionando 1.1 g de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con alcohol bencílico, como un aceite incoloro viscoso y 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo que contenía el estereoisómero (2S,3R) como una impureza. La muestra anterior se volvió a someter a las mismas condiciones de purificación de cromatografía en columna proporcionando 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S, 3S) eluye antes que el isómero (2S,3R) en las condiciones anteriores]. Isómero (2S, 3S): RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, J = 12.3, 1H), 4.43 (d, J = 12.4, 1H), 4.21 (t aparente, J = 5.2, OH), 3.22 (d, J = 10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, solapado con la señal del disolvente), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). CL (Cond. I): T_R = 2.00 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.22. Isómero (2S, 3R): RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (d, J = 7.5,

2H), 7.39-7.10 (m, 16H), 4.63 (d, *J*= 12.1, 1H), 4.50 (t aparente, J = 4.9, 1H), 4.32 (d, J = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, J = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, J = 6.8, 3H). CL (Cond. I): T_R = 1.92 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.52.

Las asignaciones estereoquímicas relativas de los productos de reducción con DIBAL se hicieron basándose en estudios NOE llevados a cabo en derivados lactona preparados a partir de cada isómero usando el siguiente protocolo: Se añadió LiHMDS (50 µl de 1.0 M/THF, 0.05 mmol) a una solución enfriada (hielo-agua) en THF (2.0 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (62.7 mg, 0.135 mmol), y la mezcla de reacción se agitó a temperatura similar durante ~2 horas. El componente volátil se eliminó a vacío y el residuo se repartió entre CH_2Cl_2 (30 ml), agua (20 ml) y solución acuosa saturada de NH_4Cl (1 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se sometió a una purificación BIOTAGE® (40 g gel de sílice; 10-15% de EtOAc/hexanos) proporcionando (3S,4S)-4-metil-3-(9-fenil-9H-fluoren-9-ilamino)dihidrofuran-2(3H)-ona como una película incolora de sólido (28.1 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a (3S,4R)-4-metil-3-(9-fenil-9H-fluoren-9-

ilamino)dihidrofuran-2(3H)-ona. Isómero (3S,4S)-lactona: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.83 (d, J = 7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (t aparente, J = 8.3, 1H), 3.60 (d, J = 5.8, NH), 3.45 (t aparente, J = 9.2, 1H), ~2.47 (m, 1H, parcialmente solapado con la señal del disolvente), 2.16 (m, 1H), 0.27 (d, J = 6.6, 3H). CL (Cond. I): T_R = 1.98 min; CL-EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.42. Isómero (3S,4R)-lactona: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.89 (d, J = 7.6, 1H), 7.85 (d, J = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, J = 9.1, 4.8, 1H), 3.76 (d, J = 8.8, 1H), 2.96 (d, J = 3.0, NH), 2.92 (dd, J = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, J = 7.0, 3H). CL (Cond. I): T_R = 2.03 min; CL-EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.49.

Se añadieron TBDEM-Cl (48 mg, 0.312 mmol) seguido por imidazol (28.8 mg, 0.423 mmol) a una solución en CH_2Cl_2 (3 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (119.5 mg, 0.258 mmol), y la mezcla se agitó en condiciones ambientales durante 14.25 horas. La mezcla de reacción se diluyó entonces con CH_2Cl_2 (30 ml) y se lavó con agua (15 ml), y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó con una BIOTAGE® (40 g gel de sílice; 5% de EtOAc/hexanos) proporcionando 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-

ilamino)butanoato de (2S,3S)-bencilo, contaminado con impurezas con base de TBDMS, como un aceite incoloro viscoso (124.4 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo. Isómero (2S,3S)-silil éter: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, J = 4.1, 1H), 7.80 (d, J = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, J = 12.4, 1H), 4.42 (d, J = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, J = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, J = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). CL (Cond. 1, donde el tiempo de ejecución de prolongó hasta 4 min): T_R = 3.26 min; CL-EM: Anal. Calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; encontrado 578.40. Isómero (2S,3R)-silil éter: RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, J = 3.0, 1H), 7.80 (d, J = 3.1, 1H), 7.39-7.10 (m, 16H), 4.66 (d, J = 12.4, 1H), 4.39 (d, J = 12.4, 1H), 3.61 (dd, J = 9.9, 5.6, 1H), 3.45 (d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

Se unió un globo de hidrógeno a una mezcla de 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (836 mg, 1.447 mmol) y Pd al 10%/C (213 mg) en EtOAc (16 ml) y la mezcla se agitó a temperatura ambiente durante ~ 21 horas, recargándose el

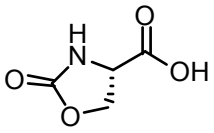
globo con H_2 cuando fue necesario. La mezcla de reacción se diluyó con CH_2Cl_2 y se filtró a través de un lecho de tierra de diatomeas (CELITE®-545), y se lavó el lecho con EtOAc (200 ml), EtOAc/MeOH (mezcla 1:1, 200 ml) y MeOH (750 ml). La fase orgánica combinada se concentró y se preparó una malla de gel de sílice a partir del material bruto resultante y se sometió a una cromatografía ultrarrápida (mezcla 8:2:1 de EtOAc/i-PrOH/H_2O) proporcionando ácido (2S,3S)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico como un sólido apelusado blanco (325 mg). Se elaboró 4-(*terc*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a ácido (2S,3R)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico. (Isómero 2S,3S)-amino ácido: RMN de ^1H (mtanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76 (dd, J = 10.5, 5.2, 1H), 3.73 (d, J = 3.0, 1H), 3.67 (dd, J = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, J = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). CL-EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44. Isómero (2S,3R)-amino ácido: RMN de ^1H (metanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, J = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, J = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44.

Se añadieron agua (1 ml) y NaOH (0.18 ml de 1.0 M/H_2O, 0.18 mmol) a una mezcla de ácido (2S,3S)-2-amino-4-

(*terc*-butildimetilsililoxi)-3-metilbutanoico (41.9 mg, 0.169 mmol) y Na_2CO_3 (11.9 mg, 0.112 mmol), y se sometió a ultrasonidos durante aproximadamente 1 minuto para efectuar la disolución de los reactivos. La mezcla se enfrió entonces con un baño de hielo-agua, se añadió cloroformiato de metilo (0.02 ml, 0.259 mmol) se durante 30 s y se continuó con agitación vigorosa a temperatura similar durante 40 minutos y luego a temperatura ambiente durante 2.7 horas. La mezcla de reacción se diluyó con agua (5 ml), se enfrió con baño de hielo-agua y se trató gota a gota con solución acuosa de HCl 1.0 N HCl (~0.23 ml). La mezcla se diluyó adicionalmente con agua (10 ml) y se extrajo con CH_2Cl_2 (15 ml, 2x). La fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando Cap-80a como un sólido blanquecino. Se elaboró ácido (2S,3R)-2-amino-4-(*terc*-butildimetilsililoxi)-3-metilbutanoico de forma similar a Cap-80b. Cap-80a: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 12.57 (s ancho, 1H), 7.64 (d, J = 8.3, 0.3H), 7.19 (d, J = 8.8, 0.7H), 4.44 (dd, J = 8.1, 4.6, 0.3H), 4.23 (dd, J = 8.7, 4.4, 0.7H), 3.56/3.53 (dos singletes, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, solapado con la señal de t-Bu), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (tres singletes solapados, 6H). CL-EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 328.46. Cap-80b: RMN de ^1H ($CDCl_3$, δ = 7.24 ppm, 400 MHz), 6.00 (d ancho, J = 6.8, 1H),

4.36 (dd, J = 7.1, 3.1, 1H), 3.87 (dd, J = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, J = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, J = 7.1, 3H), 0.90 (s, 9H), 0.08 (s, 6H). CL-EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 328.53. Los productos brutos se utilizaron sin purificación adicional.

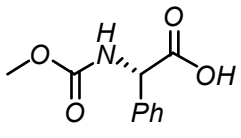
Cap-81



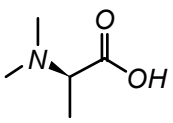
Se preparó de acuerdo con el protocolo descrito por Falb et al. Synthetic Communications, 23; 2839 (1993).

Cap-82 a Cap-85

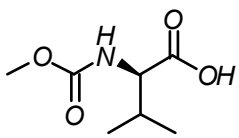
Se sintetizaron Cap-82 a Cap-85 a partir de los materiales de partida apropiados de acuerdo con el procedimiento descrito para Cap-51 o Cap-13. Las muestras presentaron perfiles espectrales similares a los de sus estereoisómeros (es decir, Cap-4, Cap-13, Cap-51 y Cap-52, respectivamente).



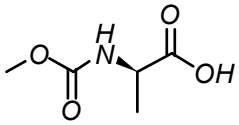
Cap-82



Cap-83

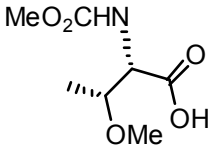


Cap-84



Cap-85

Cap-86

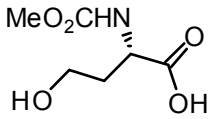


Ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico

A una mezcla de O-metil-L-treonina (3.0 g, 22.55

mmol), NaOH (0.902 g, 22.55 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (1.74 ml, 22.55 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 12 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250 ml) y MeOH al 10% en CH_2Cl_2 (250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un aceite incoloro (4.18 g, 97%) que era de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, J = 7.7 Hz, 3H). CL-EM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

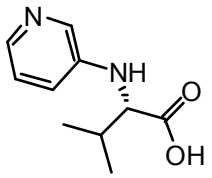
Cap-87



A una mezcla de L-homoserina (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) en H_2O (15 ml) se añadió $ClCO_2Me$ (0.76 ml, 9.79 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 48 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un sólido incoloro (0.719 g, 28%) que era de pureza suficiente para usar en las etapas siguientes. RMN de ^1H (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08-2.14 (m, 1H), 1.82-1.89 (m, 1H). CL-EM: Anal. Calculado

para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

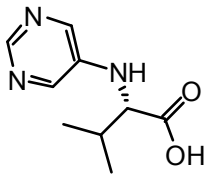
Cap-88



Se calentó una mezcla de L-valina (1.0 g, 8.54 mmol), 3-bromopiridina (1.8 ml, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) y CuI (169 mg, 0.887 mmol) en DMSO (10 ml) a 100°C durante 12h. La mezcla de reacción se enfrió hasta ta, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio iónico (Strata). La suspensión se dejó reposar durante 20 min y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25 g). Se lavó el lecho con H_2O (200 ml), MeOH (200 ml) y luego NH_3 (3M en MeOH, 2X200 ml). Se concentraron las fracciones apropiadas a vacío y el residuo (aproximadamente 1.1 g) se disolvió en H_2O, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1.02 g, 62%). RMN de ^1H (400 MHz, DMSO-d_6) δ 8.00 (s ancho, 1H), 7.68-7.71 (m, 1H), 7.01 (s ancho, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.75 (s ancho, 1H), 3.54 (s, 1H), 2.04-2.06 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H),

0.91 (d, J = 6.6 Hz, 3H). CL-EM: Anal. Calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

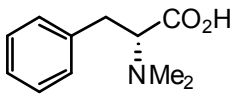
Cap-89



Se calentó a 100°C durante 12 horas una mezcla de L-valina (1.0 g, 8.54 mmol), 5-bromopirimidina (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) y CuI (179 mg, 0.94 mmol) en DMSO (10 ml). La mezcla de reacción se enfrió hasta TA, se vertió en H_2O (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio catiónico (Strata). La suspensión se dejó reposar durante 20 minutos y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25g). El lecho se lavó con H_2O (200 ml), MeOH (200 ml) y luego NH_3 (3M en MeOH, 2x200 ml). Se concentraron las fracciones apropiadas a vacío y se disolvió el residuo (aproximadamente 1.1 g) en H_2O, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1.02 g, 62%). La RMN de ^1H (400 MHz, CD_3OD) mostró que la mezcla contenía valina y no se pudo estimar la pureza. El material

se usó como tal en las posteriores reacciones. CL-EM: Anal. Calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

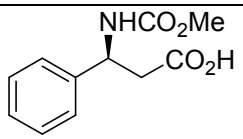
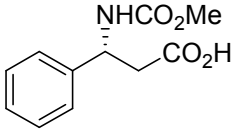
Cap-90

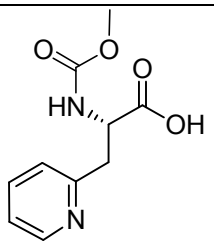
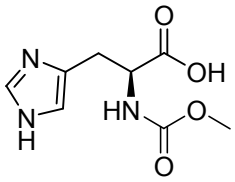
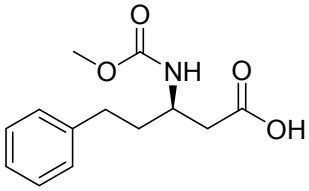
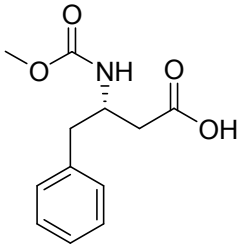
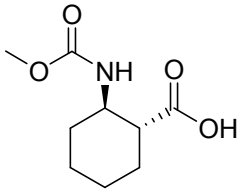
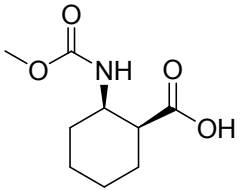


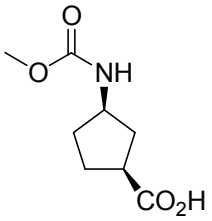
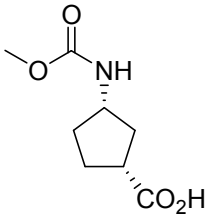
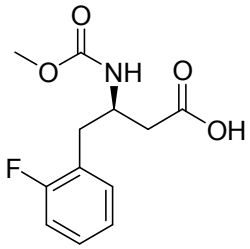
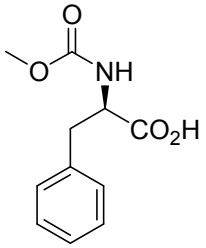
Se preparó Cap-90 de acuerdo con el procedimiento descrito para la preparación de Cap-1. El material bruto se usó como tal en las etapas posteriores. CL-EM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

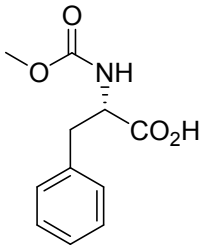
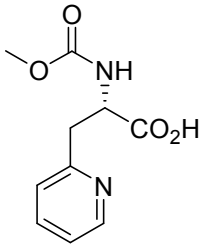
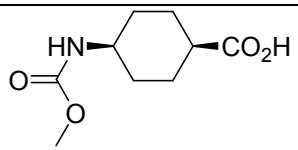
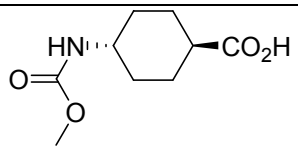
Cap-91 a Cap-116

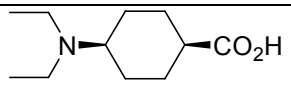
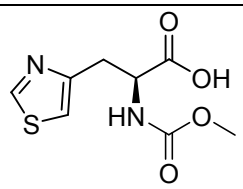
Los siguientes Caps se prepararon de acuerdo con el procedimiento del usado para la preparación del Cap-51, a menos que se indique de otro modo:

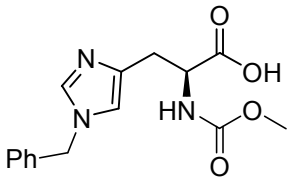
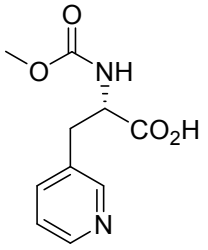
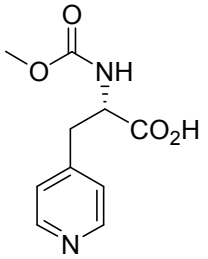
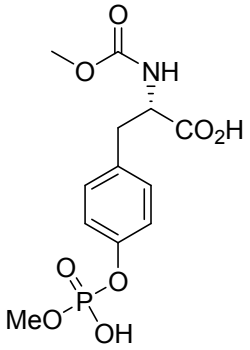
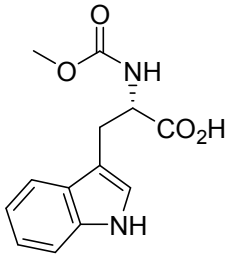
Cap	Estructura	CL-EM
Cap-91		CL-EM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Cap-92		CL-EM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.

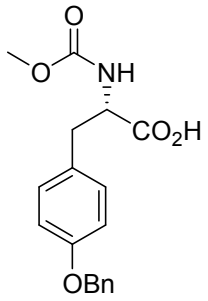
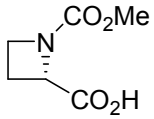
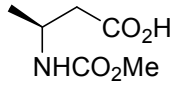
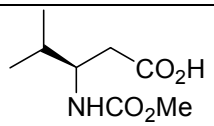
Cap	Estructura	CL-EM
Cap-93		CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-94		CL-EM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.
Cap-95		CL-EM: Anal. Calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$.
Cap-96		CL-EM: Anal. Calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$.
Cap-97		CL-EM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$.
Cap-98		CL-EM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 202 $(M+H)^+$.

Cap	Estructura	CL-EM
Cap-99		RMN de ^{1}H (400 MHz, CD_3OD) δ 3.88-3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82-1.94 (m, 3H), 1.45-1.71 (m, 2H).
Cap-99a		RMN de ^{1}H (400 MHz, CD_3OD) δ 3.88-3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82-1.94 (m, 3H), 1.45-1.71 (m, 2H).
Cap-100		CL-EM: Anal. Calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$.
Cap-101		CL-EM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.

Cap	Estructura	CL-EM
Cap-102		CL-EM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$
Cap-103		CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-104		RMN de ^1H (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50-3.53 (m, 1H), 2.66-2.69 y 2.44-2.49 (m, 1H), 1.91-2.01 (m, 2H), 1.62-1.74 (m, 4H), 1.51-1.62 (m, 2H).
Cap-105		RMN de ^1H (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33-3,35 (m, 1H, parcialmente oscurecido por disolvente), 2.37-2.41 y 2.16-2,23 (m, 1H), 1.94-2.01 (m, 4H), 1.43-1.53 (m, 2H), 1.17-1,29 (m, 2H).

Cap	Estructura	CL-EM
Cap-106	 Se preparó a partir de ácido cis-4-aminociclohexanocarboxílico y acetaldehído usando un procedimiento similar descrito para la síntesis de Cap-2. La sal HCl bruta se hizo pasar a través de MCX (lavado con $MeOH/H_2O/CH_2Cl_2$; elución con NH_3 2N /MeOH) proporcionando un aceite que se disolvió en CH_3CN/H_2O y se liofilizó proporcionando un sólido color castaño.	RMN de ^1H (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28-2.31 (m, 2H), 1.79-1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (dt aparente J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Cap-107		CL-EM: Anal. Calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$.

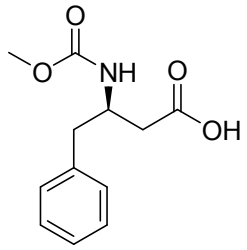
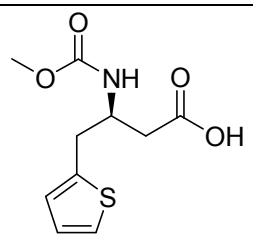
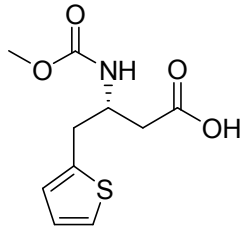
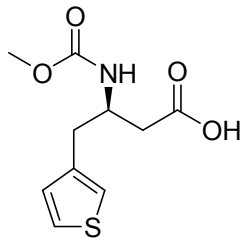
Cap	Estructura	CL-EM
Cap-108		CL-EM: Anal. Calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$.
Cap-109		CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-110		CL-EM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Cap-111		CL-EM: Anal. Calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$.
Cap-112		CL-EM: Anal. Calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$.

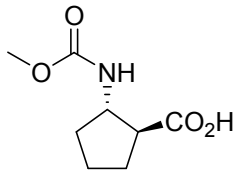
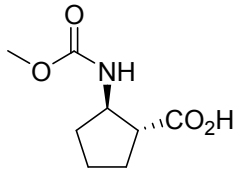
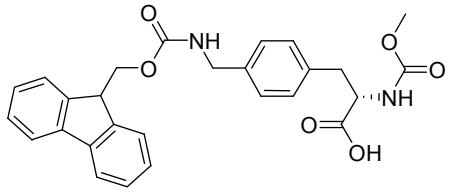
Cap	Estructura	CL-EM
Cap-113		CL-EM: Anal. Calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$.
Cap-114		RMN de ^1H (400 MHz, $CDCl_3$) δ 4.82-4.84 (m, 1H), 4.00-4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s ancho, 2H)
Cap-115		RMN de ^1H (400 MHz, $CDCl_3$) δ 5.13 (s ancho, 1H), 4.13 (s ancho, 1H), 3.69 (s, 3H), 2.61 (d, J = 5.0 Hz, 2H), 1.28 (d, J = 9.1 Hz, 3H).
Cap-116		RMN de ^1H (400 MHz, $CDCl_3$) δ 5.10 (d, J = 8.6 Hz, 1H), 3.74-3.83 (m, 1H), 3.69 (s, 3H), 2.54-2.61 (m, 2H), 1.88 (sept, J = 7.0 Hz, 1H), 0.95 (d, J = 7.0 Hz, 6H).

Cap-117 a Cap-123

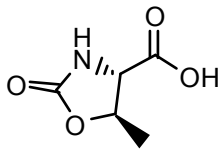
Para la preparación de Cap-117 a Cap-123 los Boc

aminoácidos se obtuvieron de suministradores comerciales y se desprotegieron por tratamiento con TFA al 25% en CH_2Cl_2. Después de completarse la reacción que se juzgó por CL-EM se eliminaron los disolventes a vacío y se carbamoiló la sal TFA correspondiente del aminoácido con cloroformiato de metilo de acuerdo con el procedimiento descrito para el Cap-51.

Cap	Estructura	CL-EM
Cap-117		CL-EM: Anal. Calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.
Cap-118		CL-EM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-119		CL-EM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Cap-120		CL-EM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.

Cap	Estructura	CL-EM
Cap-121		RMN de ^{1}H (400 MHz, $CDCl_3$) δ 4.06-4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 y 2.66 (s ancho, 1H), 1.86-2.10 (m, 3H), 1.64-1.76 (m, 2H), 1.44-1.53 (m, 1H).
Cap-122		El perfil de RMN de ^{1}H es similar al de su enantiómero, Cap-121.
Cap-123		CL-EM: Anal. Calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

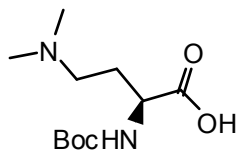
Cap-124



Se llevó a cabo la carbamoilación de la sal clorhidrato de éster *terc*-butílico de L-treonina de acuerdo con el procedimiento para Cap-51. La mezcla de reacción bruta se acidificó con HCl 1N hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 ml). Las fases orgánicas reunidas se concentraron

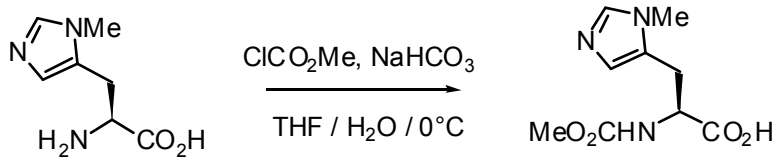
a vacío dando un aceite incoloro que solidificó en reposo. La capa acuosa se concentró a vacío y la mezcla resultante de producto y sales inorgánicas del producto y sales inorgánicas se trituró con EtOAc-CH_2Cl_2-MeOH (1:1:0.1) y luego se concentró la fase orgánica a vacío dando un aceite incoloro que por CL-EM se mostró que era el producto deseado. Ambas tandas se reunieron dando 0.52 g de un sólido. RMN de ^1H (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). CL-EM: Anal. Calculado para $C_5H_7NO_4$: 145; encontrado: 146 $(M+H)^+$.

Cap-125



A una suspensión de $Pd(OH)_2$ (20%, 100 mg), formaldehído acuoso (37% en peso, 4 ml), ácido acético (0, 5 ml) en metanol (15 ml) se añadió ácido (S)-4-amino-2-(*terc*-butoxicarbonilamino)butanoico (1 g, 4.48 mmol). La reacción se purgó varias veces con hidrógeno y se agitó durante la noche bajo un globo de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de tierra de diatomeas (CELITE®) y se eliminó el compuesto volátil a vacío. El material resultante bruto se usó como tal para la etapa siguiente. CL-EM: Anal. Calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

Cap-126



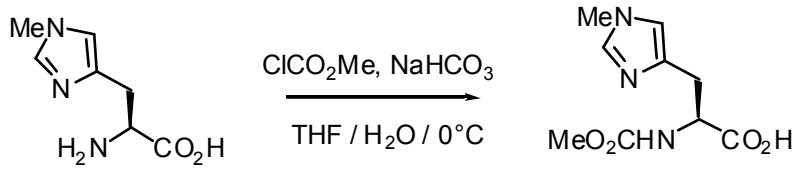
cj-25 *cap-126*

Este procedimiento es una modificación del que se usó para preparar Cap-51. A una suspensión de 3-metil-L-histidina (0.80 g, 4.70 mmol) en THF (10mL) y H_2O (10 ml) a 0°C se añadió $NaHCO_3$ (0.88 g, 10.5 mmol). La mezcla resultante se trató con $ClCO_2Me$ (0.40 ml, 5.20 mmol) y se dejó agitar la mezcla a 0°C. Después de agitar durante aproximadamente. 2h la CL-EM no mostró material de partida. La reacción se acidificó hasta pH 2 con HCl 6 N.

Los disolventes se eliminaron a vacío y el residuo se suspendió en 20 ml de MeOH al 20% en CH_2Cl_2. La mezcla se filtró y se concentró dando una espuma amarillo claro (1.21 g,). La CL-EM y RMN de ^1H mostraron que el material era una mezcla 9:1 del éster metílico y el producto deseado. Este material se suspendió en THF (10 ml) y H_2O (10 ml), se enfrió hasta 0°C y se añadió LiOH (249.1 mg, 10.4 mmol). Después de agitar aproximadamente 1h la CL-EM mostró que no quedaba éster. Seguidamente la mezcla se acidificó con HCl 6N y los disolventes se eliminaron a vacío. La CL-EM y RMN de ^1H confirmaron la ausencia del éster. El compuesto del epígrafe se obtuvo como su sal HCl contaminada con sales inorgánicas (1.91 g, >100%). El compuesto se usó como tal en posteriores

etapas sin purificación adicional. RMN de ^{1}H (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, J = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, J = 4.5, 15.6 Hz, 1H, parcialmente oscurecido por disolvente), 3.12 (dd, J = 9.0, 15.6 Hz, 1H). CL-EM: Análisis calculado para $C_9H_{13}N_3O_4$: 227.09; encontrado: 228.09 $(M+H)^+$.

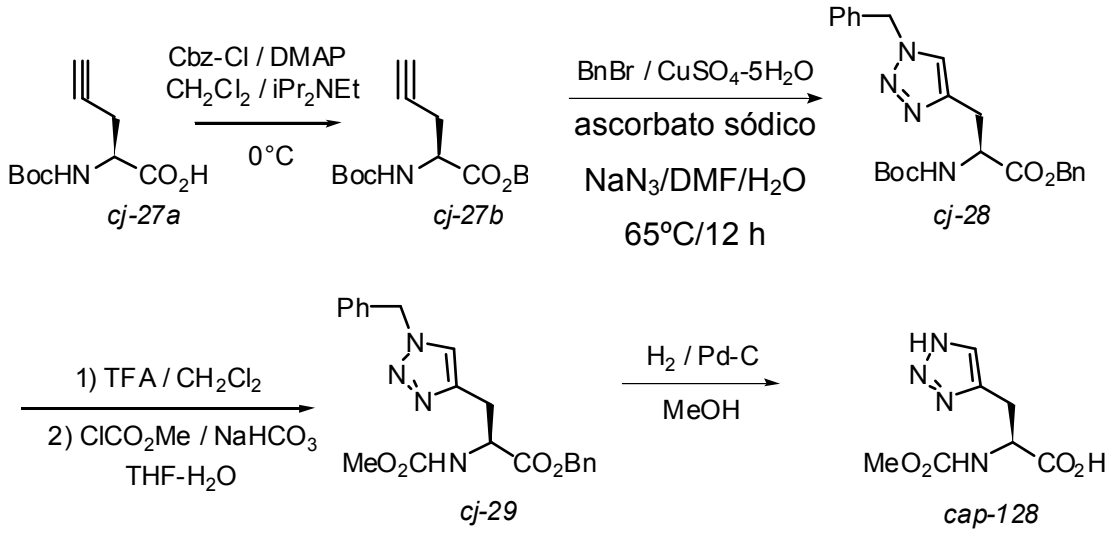
Cap-127



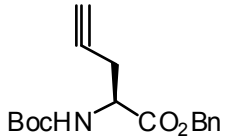
cj-26 *cap-127*

Se preparó Cap-127 de acuerdo con el procedimiento para Cap-126 anterior partiendo de ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) y $ClCO_2Me$ (0.56 ml, 7.28 mmol). El compuesto del epígrafe se obtuvo como su sal HCl (1.79 g, >100%) contaminado con sales inorgánicas. La CL-EM y RMN de ^{1}H mostraron la presencia de aproximadamente 5% del éster metílico. La mezcla bruta se usó como tal sin purificación adicional. RMN de ^{1}H (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, J = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H); CL-EM: Anal. Calculado para $C_9H_{13}N_3O_4$: 227.09; encontrado: 228 $(M+H)^+$.

Preparación de Cap-128



Etapa 1. Preparación de 2-(*terc*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).

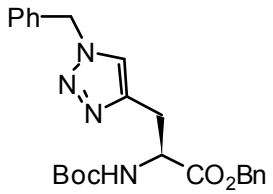


cj-27b

A una solución de cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) y iPr_2NEt (1.7 ml, 9.8 mmol) en CH_2Cl_2 (100 ml) a 0°C se añadió Cbz-Cl (0.68 ml, 4.83 mmol). La solución se dejó agitando durante 4 h a 0°C, se lavó ($KHSO_4$ 1N, salmuera), se secó (Na_2SO_4), se filtró y se concentró a vacío. El residuo se purificó por cromatografía en columna ultrarrápida (TLC 6:1 hex:EtOAc) dando el compuesto del epígrafe (1.30 g, 91%) como un aceite incoloro. RMN de ^1H (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d ancho, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48-4.53 (m, 1H), 2.68-2.81 (m, 2H), 2.00 (t, J = 2.5 Hz,

1H), 1.44 (s, 9H). CL-EM: Anal. Calculado para $C_{17}H_{21}NO_4$: 303; encontrado: 304 $(M+H)^+$.

Etapa 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(*terc*-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28).

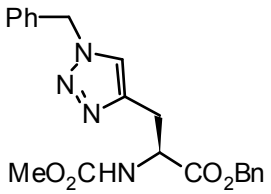


cj-28

A una mezcla de 2-(*terc*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0.50 g, 1.65 mmol), ascorbato sódico (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) y NaN_3 (0.13 g, 2.1 mmol) en DMF-H_2O (5 ml, 4:1) a ta se añadió BnBr (0.24 ml, 2.02 mmol) y la mezcla se calentó hasta 65°C. Después de 5 horas, la CL-EM indicó baja conversión. Se añadió una porción adicional de NaN_3 (100 mg) y se continuó calentando durante 12 horas. La reacción se vertió en EtOAc y H_2O y se agitó. Las fases se separaron y la fase acuosa se extrajo tres veces con EtOAc y las fases orgánicas reunidas se lavaron (H_2O x3, salmuera), se secaron (Na_2SO_4), se filtraron y concentraron. El residuo se purificó por cromatografía ultrarrápida (BIOTAGE®, 40+M 0-5% de MeOH en CH_2Cl_2; TLC 3% de MeOH en CH_2Cl_2) proporcionando un aceite amarillo claro que solidificó en reposo (748.3 mg, 104%). La RMN fue consistente con el producto deseado pero sugirió la

presencia de DMF. El material se usó como tal sin purificación adicional. RMN de ^{1}H (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27-7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, J = 1.0, 5.3 Hz, 1H), 3.06 (dd, J = 5.3, 14.7 Hz), 2.96 (dd, J = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H). CL-EM: Anal. Calculado para $C_{24}H_{28}N_4O_4$: 436; encontrado: 437 $(M+H)^+$.

Etapa 3. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29).

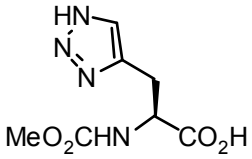


cj-29

Se añadió TFA (4 ml) a una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(*terc*-butoxicarbonilamino)propanoato de (S)-bencilo (0.52 g, 1.15 mmol) en CH_2Cl_2. La mezcla se dejó agitando a temperatura ambiente durante 2h. La mezcla se concentró a vacío dando un aceite incoloro que solidificó en reposo. Este material se disolvió en THF-H_2O y se enfrió hasta 0°C. Se añadió $NaHCO_3$ sólido (0.25 g, 3.00 mmol) seguido por $ClCO_2Me$ (0.25 ml, 3.25 mmol). Después de agitar durante 1.5h la mezcla se acidificó hasta pH~2 con HCl 6N y luego se vertió en H_2O-EtOAc. Las capas orgánicas se separaron y se extrajo la capa acuosa 2x con EtOAc. Las capas

orgánicas reunidas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío dando un aceite incoloro (505.8 mg, 111%, la RMN sugirió la presencia de una impureza no identificada) que solidificó en reposo en la bomba. El material se usó como tal sin purificación posterior. RMN de ^1H (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27-7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32-4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). CL-EM: Anal. Calculado para $C_{21}H_{22}N_4O_4$: 394; encontrado: 395 $(M+H)^+$.

Etapa 4. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (Cap-128).



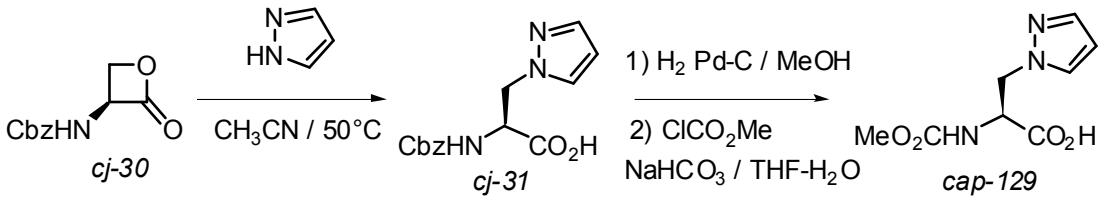
Cap-128

Se sometió 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1.11 mmol) a hidrogenación en presencia de Pd-C (82 mg) en MeOH (5 ml) a presión atmosférica durante 12h. La mezcla se filtró a través de tierra de diatomeas (CELITE®) y se concentró a vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg, 111%) que estaba contaminada con aproximadamente 10% del

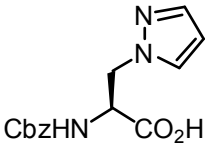
éster metílico. El material se usó sin purificación adicional.

RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.78 (s ancho, 1H), 7.59 9s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.19-4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, J = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, J = 9.9, 15.0 Hz, 1H). CL-EM: Anal. Calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

Preparación de Cap-129



Etapa 1. Preparación de ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico(cj-31).

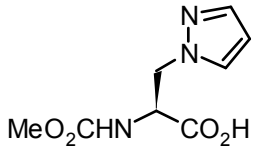


cj-31

Se calentó una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0.67 g, 3.03 mmol) y pirazol (0.22 g, 3.29 mmol) en CH_3CN (12 ml) a 50°C durante 24h. La mezcla se enfrió hasta TA durante la noche y el sólido se filtró proporcionando ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (330.1 mg). El filtrado se concentró a vacío y luego se trituró con una pequeña cantidad de CH_3CN (aproximadamente 4 ml) proporcionando una segunda

tanda (43.5 mg). Rendimiento total 370.4 mg (44%). P.f. 165.5-168°C. p.f. bibliografía 168.5-169.5°C [Vederas et al. J. Am. Chem. Soc. 1985, 107, 7105]. RMN de ^{1}H (400 MHz, CD_3OD) δ 7.51 (d, J = 2.0, 1H), 7.48 (s, J = 1.5 Hz, 1H), 7.24-7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, J = 12.7 Hz, 1H), 4.59-4.66 (m, 2H), 4.42-4,49 (m, 1H). CL-EM: Anal. Calculado para $C_{14}H_{15}N_3O_4$: 289; encontrado: 290 $(M+H)^+$.

Etapa 2. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (Cap-129).

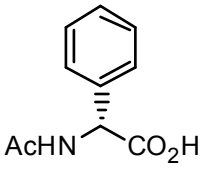


cap-129

Se sometió ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (0.20 g, 0.70 mmol) a hidrogenación en presencia de Pd-C (45 mg) en MeOH (5 ml) a presión atmosférica durante 2h. El producto parecía ser insoluble en MeOH, por tanto se diluyó la mezcla de reacción con 5 ml de H_2O y unas pocas gotas de HCl 6N. La solución homogénea se filtró a través de tierra de diatomeas (CELITE®), y el MeOH se eliminó a vacío. La solución restante se congeló y se liofilizó dando una espuma amarilla (188.9 mg). Este material se suspendió en THF-H_2O (1:1, 10 ml) y luego se enfrió hasta 0°C. A la mezcla fría se añadió $NaHCO_3$ (146.0 mg, 1.74 mmol) cuidadosamente (generación de CO_2).

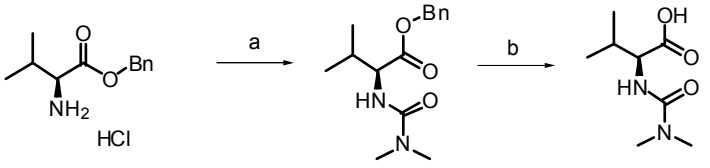
Después de cesar la generación de gas (aproximadamente 15 min) se añadió $ClCO_2Me$ (0.06 ml, 0.78 mmol) gota a gota. La mezcla se dejó agitando durante 2 horas y se acidificó hasta pH~2 con HCl 6N y se vertió en EtOAc. Las fases se separaron y la fase acuosa se extrajo con EtOAC (x5). Las fases orgánicas reunidas se lavaron (salmuera), se secaron (Na_2SO_4), se filtraron y concentraron dando el compuesto del epígrafe como un sólido incoloro (117.8 mg, 79%). RMN de ^1H (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.19 (t aparente, J = 2.0 Hz, 1H), 4.47 (dd, J = 3.0, 12.9 Hz, 1H), 4.29-4,41 (m, 2H), 3.48 (s, 3H). CL-EM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

Cap-130



Se preparó Cap-130 por acilación de (R)-fenilglicina disponible comercialmente de forma análoga al procedimiento dado en: Calmes, et al., J. Tetrahedron, 43(10): 2285 (1987).

Cap-131



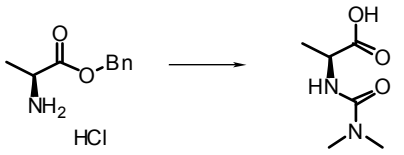
Etapa a: Se añadió cloruro de dimetilcarbamoílo

(0.92 ml, 10 mmol) lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2.44 g; 10 mmol) y base de Hunig (3.67 ml, 21 mmol) en THF (50 ml). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró a presión reducida. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El aceite amarillo resultante se purificó por cromatografía ultrarrápida, eluyendo con acetato de etilo:hexanos (1:1). Las fracciones recogidas se concentraron a vacío proporcionando 2.35 g (85%) de aceite transparente. RMN de. ^1H (300 MHz, DMSO-d_6) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). CL (Cond. 1): T_R = 1.76 min; EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; encontrado 279.03.

Etapa b: A una solución en MeOH (50 ml) del intermedio preparado antes (2.35 g; 8.45 mmol) se añadió Pd/C (10%; 200 mg) y la suspensión negra resultante se llenó con N_2 (3x) y se colocó en 10.13 kPa de H_2. La mezcla se agitó a temperatura ambiente durante la noche y se filtró a través de un filtro de microfibra para separar el catalizador. La solución transparente resultante se concentró entonces a

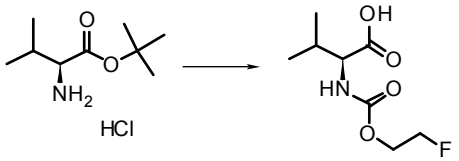
presión reducida obteniendo 1.43 g (89%) de Cap-131 como espuma blanca, que se usó sin purificación posterior. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). CL (Cond. 1): T_R = 0.33 min; EM: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.04.

Cap-132



Cap-132 se preparó a partir de clorhidrato de 2-aminopropanoato de (S)-bencilo de acuerdo con el procedimiento descrito para Cap-131. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (ct, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). CL (Cond. 1): T_R = 0.15 min; EM: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; encontrado 161.00.

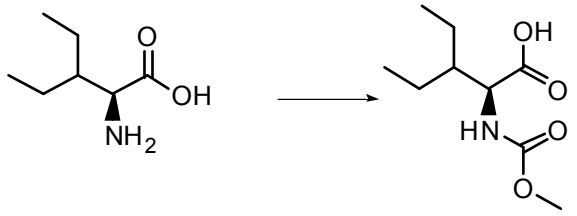
Cap-133



Cap-133 se preparó a partir de clorhidrato de 2-amino-3-metilbutanoato de (S)-*terc*-butilo y cloroformiato de 2-fluoroetilo de acuerdo con el procedimiento descrito para Cap-47. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.87 (t, J = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H),

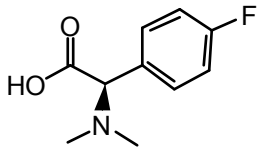
4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, J = 8.54 Hz, 1H), 12.54 (s, 1H).

Cap-134



Cap-134 se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de acuerdo con el procedimiento descrito para Cap-51. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1,38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, J = 8.85, 5.19 Hz, 1H), 7.24 (d, J = 8.85 Hz, 1H), 12.55 (s, 1H). CL (Cond. 2): T_R = 0.66 min; CL-EM: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; encontrado 204.02.

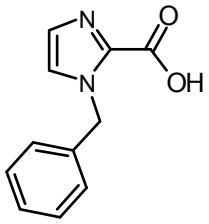
Cap-135



Una solución de ácido D-2-amino-(4-fluorofenil)acético (338 mg, 2.00 mmol), HCl 1N en éter dietílico (2.0 ml, 2.0 mmol) y formalina (37%, 1 ml) en metanol (5 ml) se sometió a hidrogenación bajo un globo en paladio al 10% sobre carbón (60 mg) durante 16 h a 25°C. La mezcla se filtró a través de CELITE® proporcionando la sal HCl de Cap-135 como una espuma blanca (316 mg, 80%). RMN de ^{1}H (300 MHz, MeOH-d_4) δ 7.59 (dd, J = 8.80, 5.10 Hz, 2H), 7.29

(t, J = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (s muy ancho, 3H), 2.63 (s muy ancho, 3H); T_R = 0.19 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; encontrado: 198.10.

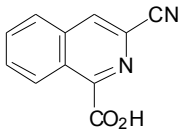
Cap-136



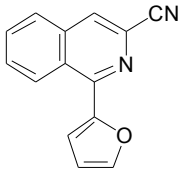
A una suspensión enfriada (-50 °C) de 1-bencil-1H-imidazol (1.58 g, 10.0 mmol) en éter dietílico anhidro (50 ml) en nitrógeno se añadió n-butil litio (2.5 M en hexanos, 4.0 ml, 10.0 mmol) gota a gota. Después de agitar durante 20 minutos a -50 °C, se hizo burbujear dióxido de carbono (pasado a través de Drierite) en la mezcla de reacción durante 10 minutos antes de dejar calentar hasta 25°C. El precipitado pesado que se formó al añadir dióxido de carbono a la mezcla de reacción se filtró proporcionando un sólido blanco higroscópico que se recogió en agua (7 ml), se acidificó hasta pH = 3, se enfrió y se indujo a cristalizar con raspado. La filtración de este precipitado dio un sólido blanco que se suspendió en metanol, se trató con HCl 1N/éter dietílico (4 ml) y se concentró a vacío. La liofilización del residuo en agua (5 ml) proporcionó la sal HCl de Cap-136, como un sólido blanco (817 mg, 40%). RMN de ^1H (300 MHz, DMSO-d_6) δ 7.94 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz,

1H), 7.50-7.31 (m, 5H), 5.77 (s, 2H); T_R = 0.51 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; encontrado: 203.11.

Cap-137



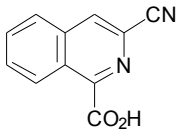
Cap-137, etapa a



Una suspensión de 1-cloro-3-cianoisoquinolina (188 mg, 1.00 mmol; preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (188 mg, 1.00 mmol), fluoruro de cesio (303.8 mg, 2.00 mmol), dicloruro de bis(tri-*terc*-butilfosfina)paladio (10 mg, 0.02 mmol) y 2-(tributilestannil)furano (378 µl, 1.20 mmol) en dioxano anhidro (10 ml) en nitrógeno se calentó a 80 °C durante 16 horas de enfriar hasta 25°C y se trató con solución acuosa saturada de fluoruro potásico con agitación vigorosa durante 1 h. La mezcla se repartió entre acetato de etilo y la fase orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con acetato de etilo de 0% a 30%/hexanos) proporcionó Cap-137, etapa a como un sólido

blanco que se usó como tal (230 mg, 105%). T_R = 1.95 min (Condiciones de EM-W2); índice de homogeneidad del 90%; EMBR: Análisis calculado para $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; encontrado: 221.12.

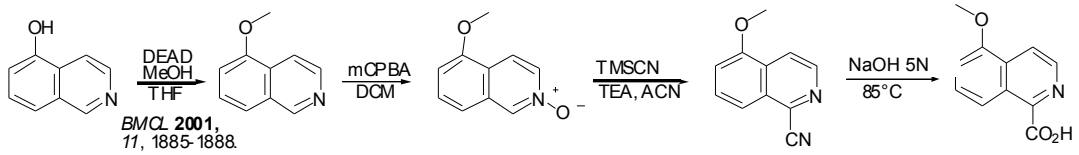
Cap-137



A una suspensión de Cap-137, etapa a, (110 mg, 0.50 mmol) y peryodato sódico (438 mg, 2.05 mmol) en tetracloruro de carbono (1 ml), acetonitrilo (1 ml) y agua (1.5 ml) se añadió tricloruro de rutenio hidratado (2 mg, 0.011 mmol). La mezcla se agitó a 25 °C durante 2 h y luego se repartió entre diclorometano y agua. La fase acuosa se separó, se extrajo dos veces más con diclorometano y se secaron los extractos reunidos sobre Na_2SO_4, se filtraron y concentraron. La trituración del residuo con hexanos proporcionó Cap-137 (55 mg, 55%) como un sólido de color grisáceo. T_R = 1.10 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; encontrado: 200.08.

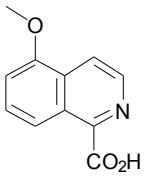
Caps-138 a Cap-158

Estrategia de síntesis. Procedimiento A.

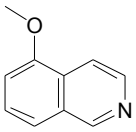


BMCL **2001**, *11*, 1885-1888.

Cap-138

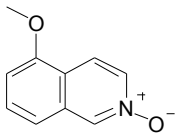


Cap-138, etapa a



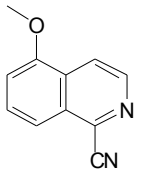
A una suspensión agitada de 5-hidroxiisoquinolina (preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (2.0 g, 13.8 mmol) y trifenilfosfina (4.3 g, 16.5 mmol) en tetrahidrofurano seco (20 ml) se añadió metanol seco (0.8 ml) y azodicarboxilato de dietilo (3.0 ml, 16.5 mmol) en varias porciones. La mezcla se agitó a temperatura ambiente durante 20 h antes de diluir con acetato de etilo y se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se preabsorbió sobre gel de sílice y se purificó (elución con acetato de etilo al 40%/hexanos) proporcionando Cap-138, etapa a como un sólido amarillo claro (1.00 g, 45%) . RMN de ^1H ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, J = 6.0 Hz, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); T_R = 0.66 min (Cond. D2); índice de homogeneidad del 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; encontrado 160.10.

Cap-138, etapa b



A una solución agitada de Cap-138, etapa a (2.34 g, 14.7 mmol) en diclorometano anhidro (50 ml) a temperatura ambiente se añadió ácido meta-cloroperbenzoico (77%, 3.42 g, 19.8 mmol) en una porción. Después de agitar durante 20 horas, se añadió carbonato potásico en polvo (2.0 g) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de que se filtrara y concentrara proporcionando Cap-138, etapa b como un sólido amarillo pálido que era suficientemente puro para usarse posteriormente (2.15 g, 83%). RMN de ^{1}H ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 7.3, 1.7 Hz, 1H), 8.04 (d, *J*=7.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.00 (s, 3H); T_R = 0.92 min, (Condiciones-D1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; encontrado: 176.0.

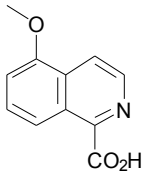
Cap-138, etapa c



A una solución agitada de Cap-138, etapa b (0.70 g, 4.00 mmol) y trietilamina (1.1 ml, 8.00 mmol) en acetonitrilo seco (20 ml) a temperatura ambiente en nitrógeno se añadió

cianuro de trimetilsililo (1.60 ml, 12.00 mmol). La mezcla se calentó a 75 °C durante 20 h antes de enfriar hasta temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución saturada de bicarbonato sódico y salmuera antes de secar sobre Na_2SO_4 y concentrar el disolvente. El residuo se sometió a cromatografía ultrarrápida sobre gel de sílice (elución con acetato de etilo al 5%/hexanos) hasta acetato de etilo al 25%/en hexanos proporcionando Cap-138, etapa c (498.7 mg) como un sólido blanco cristalino junto con 223 mg de más Cap-138, etapa c recuperado del filtrado. RMN de ^1H ($CDCl_3$, 500 MHz) δ 8.63 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 4.04 (s, 3H); T_R = 1.75 min, (Condiciones-D1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; encontrado: 185.10.

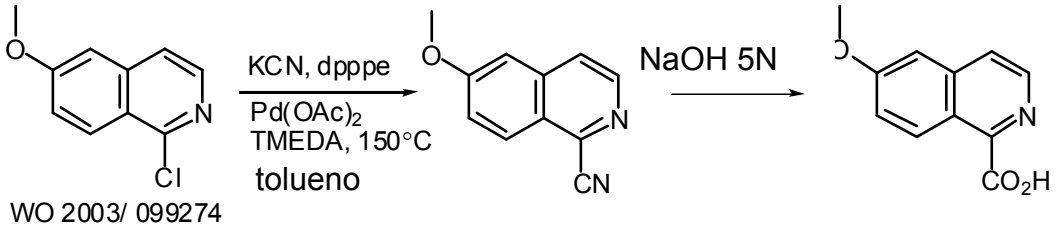
Cap-138



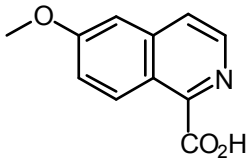
Se trató Cap-138, etapa c (0.45 g, 2.44 mmol) con solución de hidróxido sódico 5N (10 ml) y la suspensión resultante se calentó a 85°C durante 4 h, se enfrió hasta 25 °C, se diluyó con diclorometano y se acidificó con ácido clorhídrico 1N. La fase orgánica se separó, se lavó con

salmuera, se secó sobre Na_2SO_4, se concentró hasta ¼ del volumen y se filtró proporcionando Cap-138 como un sólido amarillo (0.44 g, 88.9%). RMN de ^1H (DMSO-d_6, 400 MHz) δ 13.6 (s ancho, 1H), 8.56 (d, J = 6.0 Hz, 1H), 8.16 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H); T_R = 0.70 min (Condiciones-D1); índice de homogeneidad del 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.

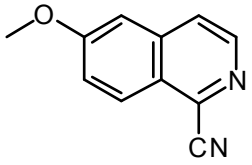
Estrategia de síntesis. Procedimiento B (derivado de Tetrahedron Letters, 42: 6707 (2001)).



Cap-139



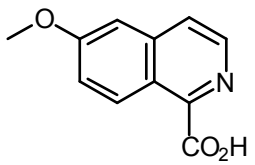
Cap-139, etapa a



A un vial a rosca de pared gruesa que contenía una suspensión desgasificada en argón de 1-cloro-6-metoxiisoquinolina (1.2 g, 6.2 mmol; preparado de acuerdo con el procedimiento del documento WO 2003/ 099274), cianuro potásico (0.40 g, 6.2 mmol), 1,5-bis(difenilfosfino)pentano

(0.27 g, 0.62 mmol) y acetato de paladio (II) (70 mg, 0.31 mmol) en tolueno anhidro (6 ml) se añadió N,N,N',N'-tetrametiletilendiamina (0.29 ml, 2.48 mmol). El vial se selló, se calentó hasta 150 °C durante 22 h y luego se dejó enfriar hasta 25 °C. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice eluyendo con acetato de etilo al 5%/hexanos hasta acetato de etilo al 25%/hexanos proporcionando Cap-139, etapa a como un sólido blanco (669.7 mg). RMN de ^1H ($CDCl_3$, 500 MHz) δ 8.54 (d, J = 6.0 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H); T_R = 1.66 min (Condiciones-D1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; encontrado: 185.20.

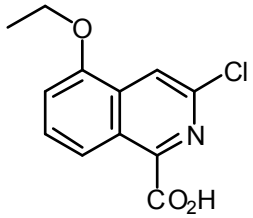
Cap-139



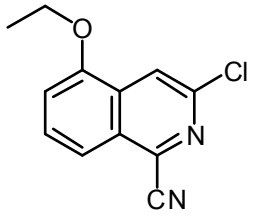
Cap-139 se preparó a partir de la hidrólisis básica de Cap-139, etapa a con NaOH 5N de acuerdo con el procedimiento descrito para Cap-138. RMN de ^1H (400 MHz, DMSO-d_6) δ 13.63 s muy ancho, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 9.3, 2.5 Hz, 1H), 3.95 (s,

3H); T_R = 0.64 min (Condiciones-D1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.

Cap-140



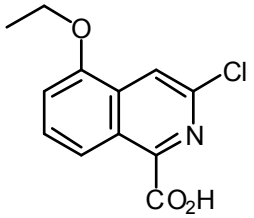
Cap-140, etapa a



A una mezcla agitada vigorosamente de 1,3-dicloro-5-etoxiisoquinolina (482 mg, 2.00 mmol; preparada de acuerdo con el procedimiento del documento WO 2005/ 051410), acetato de paladio (II) (9 mg, 0.04 mmol), carbonato sódico (223 mg, 2.10 mmol) y 1,5-bis(difenilfosfino)pentano (35 mg, 0.08 mmol) en dimetilacetamida seca (2 ml) a 25 °C en nitrógeno se añadió N,N,N',N'-tetrametiletilendiamina (60 ml, 0.40 mmol). Después de 10 min, la mezcla se calentó hasta 150 °C, y luego se añadió una solución patrón de acetona cianohidrina (preparada a partir de 457 µl de acetona cianohidrina en 4.34 ml de DMA) en porciones de 1 ml durante 18 h usando una bomba de jeringa. La mezcla se repartió entonces entre acetato de etilo y agua y se separó la fase orgánica, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El

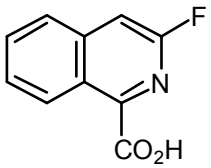
residuo se purificó sobre gel de sílice eluyendo con acetato de etilo al 10% / hexanos hasta acetato de etilo al 40% / hexanos proporcionando Cap-140, etapa a como un sólido amarillo (160 mg, 34%). T_R = 2.46 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; encontrado: 233.08.

Cap-140

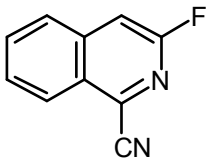


Cap-140 se preparó por la hidrólisis ácida de Cap-140, etapa a con HCl 12N como se describe en el procedimiento para la preparación de Cap-141, descrito más adelante. T_R = 2.24 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; encontrado: 252.02.

Cap-141



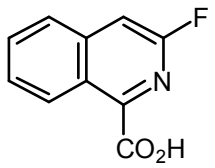
Cap-141, etapa a



Cap-141, etapa a se preparó a partir de 1-bromo-3-

fluoroisoquinolina (preparada a partir de 3-amino-1-bromoisoquinolina usando el procedimiento esbozado en J. Med. Chem., 13: 613 (1970)) como se describe en el procedimiento para la preparación de Cap-140, etapa a (vide supra). RMN de ^{1}H (500 MHz, $CDCl_3$) δ 8.35 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.83 (t, J = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); T_R = 1.60 min (Condiciones-D1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; encontrado: 172.99.

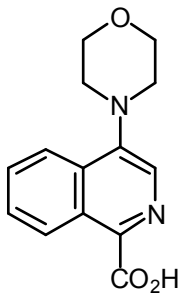
Cap-141



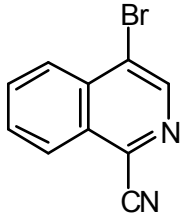
Se trató Cap-141, etapa a (83 mg, 0.48 mmol) con HCl 12N (3 ml) y la suspensión resultante se calentó a 80 °C durante 16 h antes de enfriar hasta temperatura ambiente y se diluyó con agua (3 ml). La mezcla se agitó durante 10 min y luego se filtró proporcionando Cap-141 como un sólido blanquecino (44.1 mg, 48%). El filtrado se diluyó con diclorometano y se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró proporcionando más Cap-141 que era suficientemente puro para usarlo posteriormente (29.30 mg, 32%). RMN de ^{1}H (DMSO-d_6, 500 MHz) δ 14.0 (s ancho, 1H), 8.59-8.57 (m, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); T_R = 1.33 min (Condiciones-D1); índice de

homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 191.97.

Cap-142

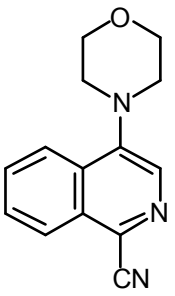


Cap-142, etapa a



Cap-142, etapa a se preparó a partir de N-óxido de 4-bromoisoquinolina como se describe en el procedimiento en dos etapas para la preparación de Cap-138, etapas b y c. T_R = 1.45 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; encontrado: 233.00.

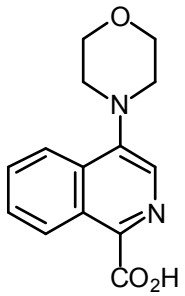
Cap-142, etapa b



A una suspensión desgasificada en argón de Cap-142,

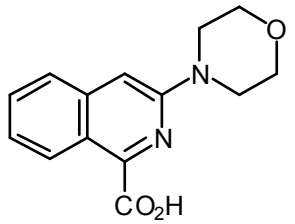
etapa a (116 mg, 0.50 mmol), fosfato potásico tribásico (170 mg, 0.80 mmol), acetato de paladio (II) (3.4 mg, 0.015 mmol) y 2-(diciclohexilfosfino)bifenilo (11 mg, 0.03 mmol) en tolueno anhidro (1 ml) se añadió morfolina (61 μl, 0.70 mmol). La mezcla se calentó a 100 °C durante 16 h, se enfrió hasta 25 °C y se filtró a través de tierra de diatomeas (CELITE®). La purificación del residuo sobre gel de sílice eluyendo con acetato de etilo del 10% a 70% / hexanos proporcionó Cap-142, etapa b (38 mg, 32%) como un sólido amarillo, que se llevó a etapas posteriores directamente. T_R = 1.26 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; encontrado: 240.13.

Cap-142

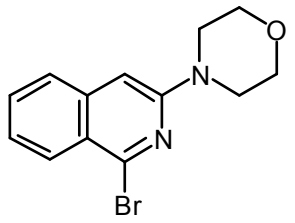


Cap-142 se preparó a partir de Cap-142, etapa b con hidróxido sódico 5N como se describe en el procedimiento para Cap-138. T_R = 0.72 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; encontrado: 259.08.

Cap-143

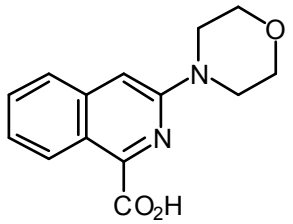


Cap-143, etapa a



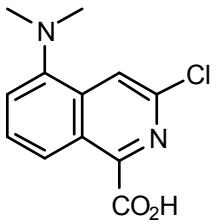
A una solución agitada de 3-amino-1-bromoisoquinolina (444 mg, 2.00 mmol) en dimetilformamida anhidra (10 ml) se añadió hidruro sódico (60%, sin lavar, 96 mg, 2.4 mmol) en una porción. La mezcla se agitó a 25 °C durante 5 min antes de añadir éter 2-bromoetílico (90%, 250 µl, 2.00 mmol). La mezcla se agitó otra vez a 25 °C durante 5 h y a 75 °C durante 72 h antes de enfriar hasta 25 °C, se inactivó con solución saturada de cloruro amónico y se diluyó con acetato de etilo. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación del residuo sobre gel de sílice eluyendo con acetato de etilo al 0% a 70% / hexanos proporcionó Cap-143, etapa a como un sólido amarillo (180 mg, 31%). T_R = 1.75 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; encontrado: 293.04.

Cap-143

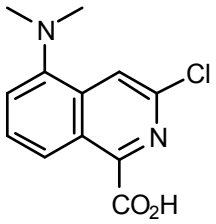


A una solución fría (-60 °C) de Cap-143, etapa a (154 mg, 0.527 mmol) en tetrahidrofurano anhidro (5 ml) se añadió una solución de n-butil litio en hexanos (2.5 M, 0.25 ml, 0.633 mmol). Después de 10 min, se burbujeó dióxido de carbono en la mezcla de reacción durante 10 minutos antes que se inactivara con HCl 1N y se dejó calentar hasta 25°C. La mezcla se extrajo entonces con diclorometano (3 x 30 ml) y los extractos orgánicos reunidos se concentraron a vacío. La purificación del residuo por una HPLC de fase inversa (MeOH/agua/TFA) proporcionó Cap-143 (16 mg, 12%). T_R = 1.10 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; encontrado: 259.08.

Cap-144



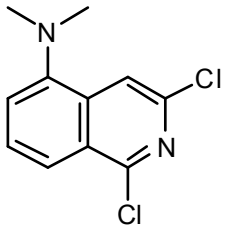
Cap-144, etapa a



Se añadió 1,3-dicloroisoquinolina (2.75 g,

13.89 mmol) en pequeñas porciones a una solución fría (0 °C) de ácido nítrico fumante (10 ml) y ácido sulfúrico concentrado (10 ml). La mezcla se agitó a 0°C durante 0.5 horas antes de que se calentara gradualmente hasta 25°C a la que se agitó durante 16 horas. La mezcla se vertió entonces en un vaso de precipitados que contenía hielo triturado y agua y la suspensión resultante se agitó durante 1 hora a 0°C antes de que se filtrara proporcionando Cap-144, etapa a (2.73 g, 81%) como un sólido amarillo que se usó directamente. T_R = 2.01 min. (Condiciones-D1); índice de homogeneidad del 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; encontrado: 242.92.

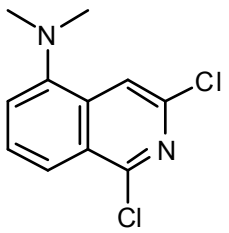
Cap-144, etapa b



Se suspendió Cap-144, etapa a (0.30 g, 1.23 mmol) en metanol (60 ml) y se trató con óxido de platino (30 mg) y la suspensión se sometió a hidrogenación de Parr a 48.26 kPa de H_2 durante 1.5 h. A continuación, se añadieron formalina (5 ml) y más óxido de platino (30 mg) y la suspensión se volvió a

someter a hidrogenación de Parr a 310.26 kPa de H_2 durante 13 h. A continuación se sometión a filtración por succión a través de tierra de diatomeas (CELITE®) y se concentró hasta ¼ de su volumen. La filtración por succión del precipitado proporcionó el compuesto del epígrafe como un sólido amarillo que se sometió a cromatografía sobre gel de sílice eluyendo con acetato de etilo al 5% en hexanos hasta acetato de etilo al 25% / hexanos proporcionando Cap-144, etapa b (231 mg, 78%) como un sólido amarillo pálido. T_R = 2.36 min (Condiciones-D1); índice de homogeneidad del 95%; RMN de ^1H (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, J = 7.3 Hz, 1H), 2.88 (s, 6H); CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; encontrado: 241.02. EMAR: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; encontrado: 241.0296.

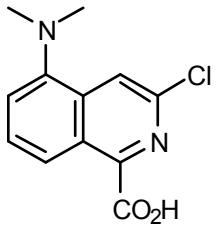
Cap-144, etapa c



Cap-144, etapa c se preparó a partir de Cap-144, etapa b de acuerdo con el procedimiento descrito para la preparación de Cap-139, etapa a. T_R = 2.19 min

(Condiciones-D1); índice de homogeneidad del 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; encontrado: 232.03. EMAR: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; encontrado: 232.0631.

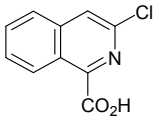
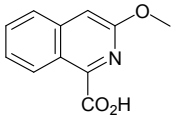
Cap-144

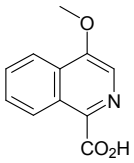
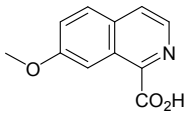


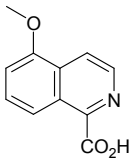
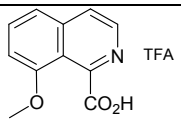
Cap-144 se preparó de acuerdo con el procedimiento descrito para Cap-141. T_R = 2.36 min (Condiciones-D1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; encontrado: 238.09.

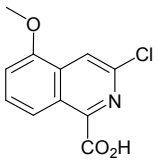
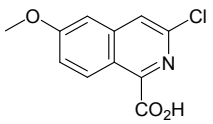
Caps-145 a Cap-162

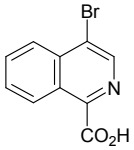
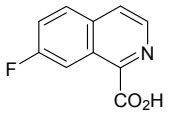
Se prepararon los Caps-145 a Cap-162 a partir de las 1-cloroisoquinolinas apropiadas de acuerdo con el procedimiento descrito para la preparación de Cap-138 (Procedimiento A) o Cap-139 (Procedimiento B) a no ser que se describa de otro modo más adelante.

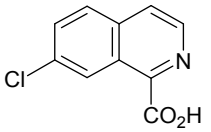
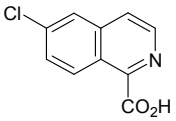
Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-145	 Preparado a partir de 1,3-dicloroisoquinolina disponible comercialmente	B	12N HCl	1.14 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.00.
Cap-146	 Preparado a partir de 3-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	1.40 min (Condiciones-D1); 95% ; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.06.

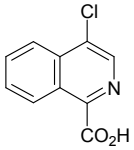
Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-147	 Preparado a partir de 1-cloro-4-hidroxiisoquinolina disponible comercialmente	B	NaOH 5N	0.87 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.
Cap-148	 Preparado a partir de 7-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0.70 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.

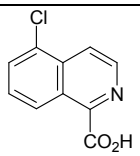
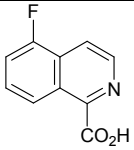
Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-149	 Preparado a partir de 5-hidroxiisoquinolina disponible comercialmente	A	NaOH 5N	0.70 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.05.
Cap-150	 Preparado a partir de 8-metoxi-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	A	HCl 12N	0.26 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 204.04.

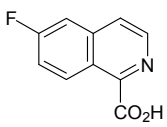
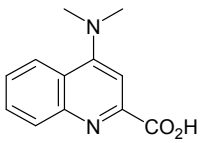
Cap nº	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-151 ácido 3-cloro-5-metoxiisoquinolin-1-carboxílico	 Preparado a partir de 5-metoxi-1,3-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2005 / 051410.	B	HCl 12N	1.78 min (Condiciones-D1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; encontrado: 238.09.
Cap-152	 Preparado a partir de 6-metoxi-1,3-dicloroisoquinolina disponible comercialmente	B	HCl 12N	1.65 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; encontrado: 238.09.

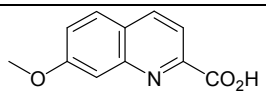
Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-153	 Preparado a partir de 4-bromoisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/062241	A	HCl 6N	1.18 min (Condiciones de EM-W1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; encontrado: 251.95.
Cap-154	 Preparado a partir de 7-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	B	NaOH 5N	0.28 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.

Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-155	 Preparado a partir de 1,7-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	B	NaOH 5N	0.59 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.00.
Cap-156	 Preparado a partir de 1,6-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	B	NaOH 5N	0.60 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.03.

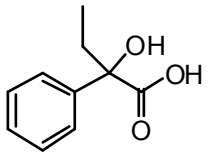
Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-157	 Preparado a partir de 1,4-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/062241	B	HCl 12N	1.49 min (Condiciones-D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; encontrado: 208.00.

Cap n°	Cap	Proce-dimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-158	 Preparado a partir de 1,5-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	B	NaOH 5N	0.69 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; encontrado: 208.01.
Cap-159	 Preparado a partir de 5-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274	B	NaOH 5N	0.41 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.

Cap n°	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-160	 Preparado a partir de 6-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274	B	NaOH 5N	0.30 min (Condiciones de EM-W1); 90%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; encontrado: 192.03.
Cap-161	 Preparado a partir de ácido 4-bromoquinolin-2-carboxílico y dimetilamina (DMSO, 100 °C)	--	--	0.70 min (Cond. D1); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; encontrado: 217.06.

Cap n°	Cap	Procedimiento	Hidrólisis	T_r (Condición de CL); índice de homogeneidad, %; datos EM
Cap-162	 Preparado a partir de m-anisidina siguiendo el procedimiento descrito en J. Hetero. Chem., 17 (1993) y Heterocycles, 60: 953 (2003).	--	--	0.65 min (Condiciones-M3); 95%; CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; encontrado: 203.94.

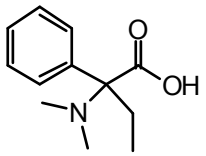
Cap-163



A una solución de ácido 2-cetobutírico (1.0 g, 9.8 mmol) en éter dietílico (25 ml) se añadió gota a gota bromuro de fenilmagnesio (22 ml, 1M en THF). La reacción se agitó a ~25 °C en nitrógeno durante 17.5h. La reacción se acidificó con HCl 1N y el producto se extrajo con acetato de etilo (3 x 100 ml). La fase orgánica reunida se lavó con agua seguido por salmuera y se secó sobre $MgSO_4$. Después de concentrar a

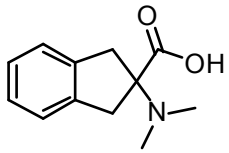
vacío se obtuvo un sólido blanco. El sólido se recristalizó en hexanos/acetato de etilo proporcionando Cap-163 como agujas blancas (883.5 mg). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.71 (s ancho, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (s ancho, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (t ap, J = 7.4 Hz, 3H).

Cap-164



Se expuso a H_2 a 344.74 kPa en un frasco de Parr durante 42 horas una mezcla de ácido 2-amino-2-fenilbutírico (1.5 g, 8.4 mmol), formaldehído (14 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (0.5 mg) en MeOH (40 ml). La reacción se filtró sobre CELITE® y se concentró a vacío, el residuo se suspendió en MeOH (36 ml) y el producto se purificó con una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de Cap-164 como un sólido blanco (1.7 g). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (t ap, J = 7.3 Hz, 3H).

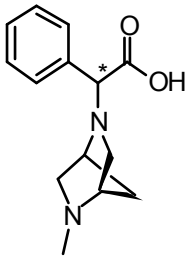
Cap-165



A una mezcla de ácido 2-amino-2-indanocarboxílico (258.6 mg, 1.46 mmol) y ácido fórmico (0.6 ml, 15.9 mmol) en 1,2-dicloroetano (7 ml) se añadió formaldehído (0.6 ml, 37%

en agua). La mezcla se agitó a ~25 °C durante 15 min luego se calentó a 70 °C durante 8h. El componente volátil se eliminó a vacío y el residuo se disolvió en DMF (14 ml) y se purificó por una HPLC de fase inversa (MeOH/H_2O/TFA) proporcionando la sal TFA de Cap-165 como un aceite viscoso (120.2 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; encontrado: 206.07.

Cap-166a y Cap-166b

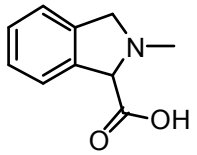


Cap-166a: Diastereómero-1
Cap-166b: Diastereómero-2

Caps-166a y Cap-166b se prepararon a partir de (1S, 4S)-(+)-2-metil-2,5-diazabiciclo[2.2.1]heptano (2HBr) de acuerdo con el procedimiento descrito para la síntesis de Cap-7a y Cap-7b, con la salvedad de que se separó el éster bencílico intermedio usando una columna semipreparativa CHIRALCEL®OJ, 20 x 250 mm, 10 μm eluyendo con una mezcla 85:15 de heptano/etanol a 10 ml/min de caudal de elución durante 25 min. Cap-166b: RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (s ancho ap, 1H), 3.16 (s ancho ap, 1H), 2.83 (d, *J*=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H),

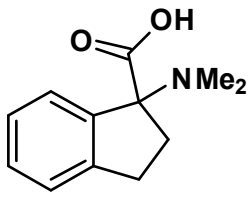
1.77 (d, J = 9.8 Hz, 1H), 1.63 (d, J = 9.8 Hz, 1H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; encontrado: 247.11.

Cap-167



Se agitó una solución de ácido Boc-1,3-dihidro-2H-isoindol carboxílico racémico (1.0g, 3.8 mmol) en TFA al 20%/CH_2Cl_2 a ~25 °C durante 4h. Se eliminó todo el componente volátil a vacío. Se expuso una mezcla del material bruto resultante, formaldehído (15 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (10 mg) en MeOH a H_2 (275.71 kPa) en un frasco de Parr durante 23 h. La mezcla de reacción se filtró sobre CELITE® y se concentró a vacío proporcionando Cap-167 como una espuma amarilla (873.5 mg). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; encontrado: 178.65.

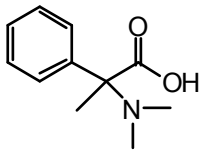
Cap-168



Se preparó Cap-168 racémico a partir de ácido Boc-aminoindano-1-carboxílico racémico de acuerdo con el

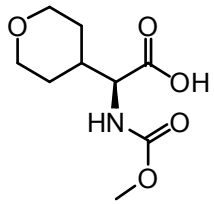
procedimiento descrito para la preparación de Cap-167. El producto bruto se usó como tal.

Cap-169



Se colocó una mezcla de clorhidrato de ácido 2-amino-2-fenilpropanoico (5.0 g, 2.5 mmol), formaldehído (15 ml, 37% en agua), HCl 1N (15 ml) y Pd al 10%/C (1.32 g) en MeOH (60 ml) en un frasco de Parr y se agitó en hidrógeno (379.11 kPa) durante 4 días. La mezcla de reacción se filtró sobre Celite y se concentró a vacío. El residuo se suspendió en MeOH y se purificó por HPLC preparativa de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA de Cap-169 como un semisólido viscoso (2.1 g). RMN de ^1H ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 7.58-7.52 (m, 2 H), 7.39-7.33 (m, 3H), 2.86 (s ancho, 3H), 2.47 (s ancho, 3H), 1.93 (s, 3H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; encontrado: 194.12.

Cap-170

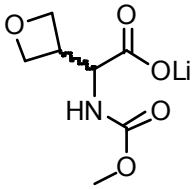


Ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético

A ácido (S)-2-amino-2-(tetrahidro-2H-piran-4-il)acético (505 mg; 3.18 mmol; obtenido de Astatech) en agua

(15ml) se añadió carbonato sódico (673 mg; 6.35 mmol) y la mezcla resultante se enfrió hasta 0°C momento en el que se añadió cloroformiato de metilo (0.26ml; 3.33mmol) gota a gota durante 5 minutos. Se dejó agitando la reacción durante 18 horas llegando lentamente a temperatura ambiente a medida que se fundía el baño de hielo. La mezcla de reacción se repartió entonces entre HCl 1N y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo de nuevo con dos porciones más de acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando Cap-170 un residuo incoloro. RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 12.65 (1 H, s ancho), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2 H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); CL-EM: Análisis calculado para $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; encontrado 218.1.

Cap-171



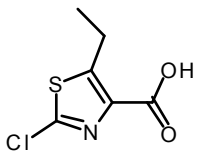
Una solución de 2-(benciloxicarbonilamino)-2-(oxetan-3-iliden)acetato de metilo (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609–613) en acetato de etilo (7 ml) y CH_2Cl_2 (4.00 ml) se desgasificó burbujeando nitrógeno durante

10min. Se añadieron entonces dicarbonato de dimetilo (0.116 ml, 1.082 mmol) y Pd/C (20 mg, 0.019 mmol), la mezcla de reacción se ajustó bajo un globo de hidrógeno y se dejó agitando a temperatura ambiente durante la noche momento en el que la TLC (95:5 CH_2Cl_2 / MeOH: visualizada con tinción realizada en 1g de $Ce(NH_4)_2SO_4$, 6g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua) indicó la conversión completa. La reacción se filtró a través de CELITE® y se concentró. El residuo se purificó por BIOTAGE® (cada con diclorometano en 25 de muestra; elución en columna 25S con diclorometano para 3CV luego 0 a 5% de MeOH / diclorometano sobre 250ml luego mantenido a 5% de MeOH / diclorometano para 250 ml; fracciones de 9 ml). Las fracciones obtenidas que contenían material deseado y se concentraron hasta 120 mg (81%) de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo como un aceite incoloro. RMN de ^1H (500 MHz, cloroformo-d) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (s ancho, 1 H). CL-EM: Análisis calculado para $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; encontrado 204.0.

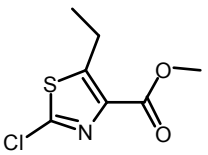
Se añadió a 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo (50 mg, 0.246 mmol) en THF (2 ml) y agua (0.5 ml) hidróxido de litio monohidratado (10.33 mg, 0.246 mmol). La solución resultante se dejó agitando durante la noche a temperatura ambiente. La TLC (1:1 EA / Hex; tinción

de Hanessian [1g de $Ce(NH_4)_2SO_4$, 6 g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua]) indicó que quedaba ~10% de material de partida. Se añadieron otros 3 mg de LiOH y se dejó agitando durante la noche momento en el que la TLC mostró que no quedaba material de partida. Se concentró a vacío y se colocó en alto vacío durante la noche proporcionando 55 mg de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de litio como un sólido incoloro. RMN de ^1H (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

Cap-172



Cap-172, etapa a



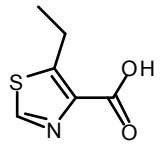
La siguiente etapa de diazotación se adaptó de Barton, A. et al., J. C. S. Perkin Trans I, 159-164 (1982): Se añadió una solución de $NaNO_2$ (166 mg, 2.4 mmol) en agua (0.6 ml) a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1.0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) y H_2SO_4 (5.5 ml) en agua (7.5 ml). La mezcla se agitó a 0 °C durante 45 min y se dejó calentar hasta temperatura ambiente

donde se agitó durante otra 1 h antes de añadir CuCl (118 mg). Esta mezcla se agitó de nuevo a temperatura ambiente durante 16 h antes de diluirse con salmuera y extraerse con éter dos veces. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 2-cloro-5-etiltiazol-4-carboxilato de metilo (es decir, Cap-172, etapa a) (175 mg, 85%) como un aceite naranja (80% de pureza) que se usó directamente en la siguiente reacción. T_R = 1.99 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; encontrado: 206.05.

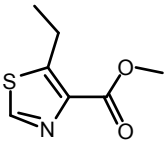
Cap-172

A una solución de 2-cloro-5-etiltiazol-4-carboxilato de metilo (175 mg) en THF/H_2O/MeOH (20 ml/ 3 ml/ 12 ml) se añadió LiOH (305 mg, 12.76 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando Cap-172 (60 mg, 74%) como un sólido rojo que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, J = 7.4 Hz), 1.23 (3 H, t, J = 7.5 Hz). T_R = 1.78 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; encontrado: 191.99.

Cap-173



Cap-173, etapa a

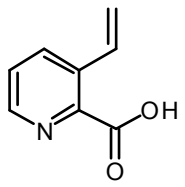


La siguiente etapa de diazotación se adaptó de Barton, A. et al., J. C. S. Perkin Trans I, 159-164 (1982): Se añadió una solución de $NaNO_2$ (150 mg, 2.17 mmol) en agua (1.0 ml) gota a gota a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1.0 mmol) en H_3PO_2 al 50% (3.2 ml). La mezcla se agitó a 0 °C durante 1 h y se dejó calentar hasta temperatura ambiente donde se agitó durante otras 2h. Después de volver a enfriar hasta 0 °C, la mezcla se trató lentamente con una solución de NaOH (85 mg) en agua (10 ml). La mezcla se diluyó entonces con solución saturada de $NaHCO_3$ y se extrajo dos veces con éter. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 5-etiltiazol-4-carboxilato de metilo (es decir, Cap-173, etapa a) (134 mg, 78%) como un aceite naranja (85% de pureza) que se usó directamente en la siguiente reacción. T_R = 1.58 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; encontrado: 172.05.

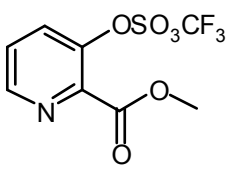
Cap-173

A una solución de 5-etiltiazol-4-carboxilato de metilo (134 mg) en THF/H_2O/MeOH (18 ml/ 2.7 ml/ 11 ml) se añadió LiOH (281 mg, 11.74 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando Cap-173 (90 mg, 73%) como un sólido naranja que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 12.74-13.04 (1 H, m), 3.20 (2 H, q, J = 7.3 Hz), 1.25 (3 H, t, J = 7.5 Hz). T_R = 1.27 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_6H_8NO_2S$: 158.03; encontrado: 158.04.

Cap-174



Cap-174, etapa a



Se añadió anhídrido tríflico (5.0 g, 18.0 mmol) gota a gota a una solución fría (0 °C) de 3-hidroxipicolinato de metilo (2.5 g, 16.3 mmol) y TEA (2.5 ml, 18.0 mmol) en

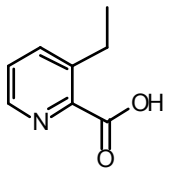
CH_2Cl_2 (80 ml). La mezcla se agitó a 0 °C durante 1h antes de dejar calentar hasta temperatura ambiente, momento en el que se agitó durante una hora más. La mezcla se inactivó entonces con solución saturada de $NaHCO_3$ (40 ml) y la fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró dando 3-(trifluorometilsulfoniloxi)picolinato de metilo (es decir, Cap-174, etapa a) (3.38 g, 73%) como un aceite marrón oscuro (>95% de pureza) que se usó directamente sin purificación posterior. RMN de ^1H (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, J = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). T_R = 1.93 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; encontrado: 286.08.

Cap-174

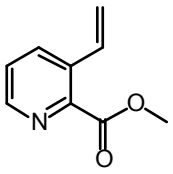
A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (570 mg, 2.0 mmol) en DMF (20 ml) se añadió LiCl (254 mg, 6.0 mmol), tributil(vinil)estannano (761 mg, 2.4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0.06 mmol). La mezcla se calentó a 100 °C durante la noche antes d añadir una solución saturada de KF (20 ml) a la mezcla de reacción a temperatura ambiente. Esta mezcla se agitó durante 4 h antes de filtrar a través de CELITE® y el lecho de CELITE® se lavó con acetato de etilo. La fase acuosa del filtrado se separó entonces y se concentró a vacío. El residuo se trató con HCl 4N en dioxanos

(5 ml) y la mezcla resultante se extrajo con metanol, se filtró y se evaporó proporcionando Cap-174 (260 mg) como un sólido verde que estaba ligeramente contaminado con sales inorgánicas pero que se usó sin purificación posterior. RMN de ^{1}H (300 MHz, DMSO-d_6) δ ppm 8.21 (1 H, d, J = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, J = 7.7, 4.8 Hz), 6.98 (1 H, dd, J = 17.9, 11.3 Hz), 5.74 (1 H, dd, J = 17.9, 1.5 Hz), 5.20 (1 H, d, J = 11.0 Hz). T_R = 0.39 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_8H_8NO_2$: 150.06; encontrado: 150.07.

Cap-175



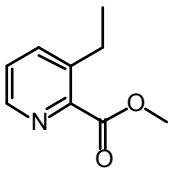
Cap-175, etapa a



A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (es decir, Cap-174, etapa a) (570 mg, 2.0 mmol), un intermedio en la preparación de Cap-174, en DMF (20 ml) se añadió LiCl (254 mg, 6.0 mmol), tributil(vinil)estannano (761 mg, 2.4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0.06 mmol). La mezcla se calentó a 100 °C durante 4 h antes de eliminar

el disolvente a vacío. El residuo se suspendió en acetonitrilo (50 ml) y hexanos (50 ml) y la mezcla resultante se lavó dos veces con hexanos. Se separó entonces la fase de acetonitrilo, se filtró a través de CELITE® y se evaporó. La purificación del residuo por cromatografía ultrarrápida en un aparato Horizon (elución con gradiente de acetato de etilo al 25% en hexanos hasta acetato de etilo al 65% en hexanos) proporcionó 3-vinilpicolinato de metilo (es decir, Cap-175, etapa a) (130 mg, 40%) como un aceite amarillo. RMN de ^{1}H (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, J = 4.6, 1.7 Hz), 7.94 (1 H, d, J = 7.7 Hz), 7.33-7.51 (2 H, m), 5.72 (1 H, d, J = 17.2 Hz), 5.47 (1 H, d, J = 11.0 Hz), 3.99 (3 H, s). T_R = 1.29 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; encontrado: 164.06.

Cap-175, etapa b



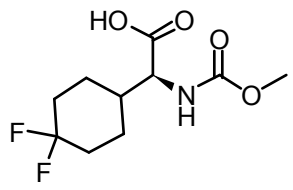
Se añadió paladio sobre carbón (10%, 25 mg) a una solución de 3-vinilpicolinato de metilo (120 mg, 0.74 mmol) en etanol (10 ml). La suspensión se agitó a temperatura ambiente en una atmósfera de hidrógeno durante 1 h antes de filtrar a través de CELITE®y se lavó el lecho de CELITE®con metanol. El filtrado se concentró hasta sequedad proporcionando 3-etilpicolinato de metilo

(es decir, Cap-175, etapa b) que se llevó directamente a la siguiente reacción. T_R = 1.15 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; encontrado: 166.09.

Cap-175

A una solución de 3-etilpicolinato de metilo en THF/H_2O/MeOH (5 ml/ 0.75 ml/ 3 ml) se añadió LiOH (35 mg, 1.47 mmol). La mezcla se agitó a temperatura ambiente durante 2 días antes de añadir más LiOH (80 mg). Después de otras 24 horas más a temperatura ambiente, la mezcla se filtró y el disolvente se eliminó a vacío. El residuo se trató entonces con HCl 4N en dioxanos (5 ml) y la suspensión resultante se concentró hasta sequedad proporcionando Cap-175 como un sólido amarillo que se usó sin purificación posterior. RMN de ^1H (300 MHz, DMSO-d_6) δ ppm 8.47 (1 H, dd, J = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, J = 7.7, 4.8 Hz), 2.82 (2 H, q, J = 7.3 Hz), 1.17 (3 H, t, J = 7.5 Hz). T_R = 0.36 min (Condición-MD1); CL-EM: Análisis calculado para $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; encontrado: 152.10.

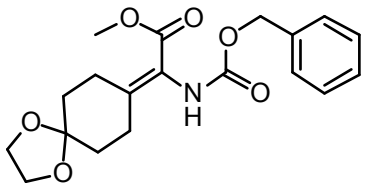
Cap-176



Ácido (S)-2(4,4-difluorociclohexil)-2-

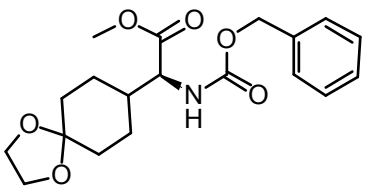
(metoxicarbonilamino)acético

Cap-176, etapa a



Se añadió una solución de 1,4-dioxaspiro[4.5]decan-8-ona (15 g, 96 mmol) en EtOAc (150 ml) a una solución de 2-(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (21.21 g, 64.0 mmol) en 1,1,3,3-tetrametilguanidina (10.45 ml, 83 mmol) y EtOAc (150 ml). La solución resultante se agitó a temperatura ambiente durante 72 h y luego se diluyó con EtOAc (25 ml). La fase orgánica se lavó con HCl 1N (75 ml), H_2O (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por BIOTAGE® (EtOAc al 5% hasta 25 %/Hexanos; 300g columna). Las fracciones reunidas que contenían el producto se concentraron entonces a vacío y el residuo se volvió a cristalizar en hexanos/EtOAc dando cristales blancos que corresponden a 2-(benciloxicarbonilamino)-2-(1,4-dioxaspiro[4.5]decan-8-iliden)acetato de metilo (6.2 g) RMN de ^1H (400 MHz, $CDCl_3$-d) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, s ancho), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, s ancho), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). CL (Cond. OL1): T_R = 2.89 min. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; encontrado: 745.47

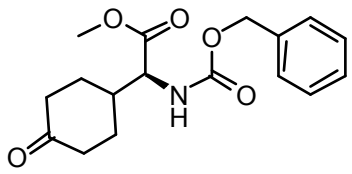
Cap-176, etapa b



Se preparó el éster Cap-176, etapa b a partir del alqueno Cap-176, etapa a de acuerdo con el procedimiento de Burk, M. et al., (J. Am. Chem. Soc., 117: 9375-9376 (1995) y referencias en el mismo): Se cargó una botella a alta presión de 500 ml con el alqueno Cap-176, etapa a (3.5 g, 9.68 mmol) en MeOH desgasificado (200 ml) en una capa de N_2. La solución se cargó entonces con tetrafluoroborato de (-)-1,2-bis((2S,5S)-2,5-dimetilfosfolano)etano(ciclooctadieno)rodio (I) (0.108 g, 0.194 mmol) y la mezcla resultante se cubrió con N_2 (3x) y se cargó con H_2 (3x). La solución se agitó vigorosamente a 482 kPa de H_2 a temperatura ambiente durante 72 h. El disolvente se eliminó a presión reducida y el residuo que quedó se suspendió en EtOAc. La solución pardusca se filtró entonces a través de un lecho de gel de sílice y se eluyó con EtOAc. El disolvente se concentró a vacío proporcionando un aceite transparente que correspondía al éster Cap-176, etapa b (3.4 g), RMN de ^1H (500 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). CL (Cond. OL1): T_R = 1.95 min. CL-EM: Análisis

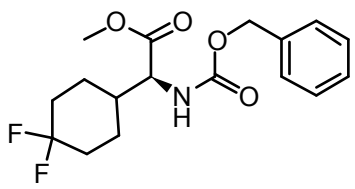
calculado para $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; encontrado: 364.27.

Cap-176, etapa c



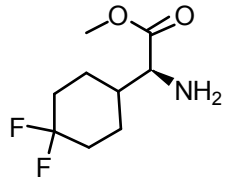
Se disolvió el éster Cap-176, etapa b (4.78 g, 13.15 mmol) en THF (15 ml) seguido por la adición secuencial de agua (10 ml), ácido acético glacial (26.4 ml, 460 mmol) y ácido dicloroacético (5.44 ml, 65.8 mmol). La mezcla resultante se agitó durante 72 h a temperatura ambiente, y la reacción se inactivó mediante la adición lente de Na_2CO_3 sólido con agitación vigorosa hasta que no fue visible la generación de gas. El producto bruto se extrajo en acetato de etilo al 10%-diclorometano y las fases orgánicas se reunieron, se secaron ($MgSO_4$), se filtraron y concentraron. El residuo resultante se purificó por BIOTAGE® (EtOAc al 0 hasta 30%/Hex; 25 g de columna) proporcionando la cetona Cap-176, etapa c (3.86g) como un aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$-d) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd, *J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). CL (Cond. OL1): T_R = 1.66 min. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; encontrado: 342.10.

Cap-176, etapa d



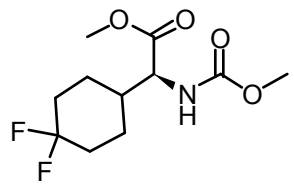
Se añadió Deoxo-Fluor® (3.13 ml, 16.97 mmol) a una solución de la cetona Cap-176, etapa c (2.71 g, 8.49 mmol) en CH_2Cl_2 (50 ml) seguido por la adición de una cantidad catalítica de EtOH (0.149 ml, 2.55 mmol). La solución amarillenta resultante se agitó a ta durante la noche. La reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado (25 ml) y la mezcla se extrajo con EtOAc (3X75 ml)). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se secaron dando un aceite amarillento. El residuo se purificó por cromatografía en BIOTAGE® (EtOAc al 2% hasta 15%/Hex; 90g de columna) y se recuperó un sólido blanco correspondiente al difluoruro de difluoro aminoácido Cap-176, etapa d (1.5 g). RMN de ^1H (400 MHz, $CDCl_3$-d) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). RMN de ^{19}F (376 MHz, $CDCl_3$-d) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). CL (Cond. OL1): T_R = 1.66 min. CL-EM: Análisis calculado para $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; encontrado: 705.18.

Cap-176, etapa e



Se disolvió el difluoruro Cap-176, etapa d (4 g, 11.72 mmol) en MeOH (120 ml) y se cargó con Pd/C (1.247 g, 1.172 mmol). Se inyectó en la suspensión N_2 (3x) y la mezcla de reacción se colocó bajo una presión de 101 kPa de H_2 (globo). La mezcla se agitó a temperatura ambiente durante 48 h. La suspensión se filtró entonces a través de un lecho de CELITE®y se concentró a vacío dando un aceite que corresponde al aminoácido Cap-176, etapa e (2.04 g) y que se usó sin purificación posterior. RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). RMN de ^{19}F (376 MHz, DMSO-d_6) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). RMN de ^{13}C (101 MHz, DMSO-d_6) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, s ancho), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). CL (Cond. OL2): T_R = 0.95 min. CL-EM: Análisis calculado para $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; encontrado: 415.40.

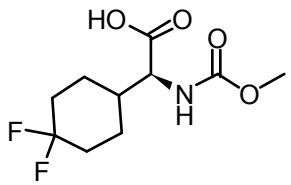
Cap-176, etapa f



Se añadió cloroformiato de metilo (1.495 ml, 19.30

mmol) a una solución de aminoácido Cap-176, etapa e (2 g, 9.65 mmol) y DIEA (6.74 ml, 38.6 mmol) en CH_2Cl_2 (100 ml). La solución resultante se agitó a ta durante 3 h y se eliminaron los volátiles a presión reducida. El residuo se purificó por BIOTAGE® (EtOAc al 0% hasta 20%/Hex; 90 g de columna). Se recuperó un aceite transparente que solidificó en reposo a vacío y que correspondía al carbamato Cap-176, etapa f (2.22 g). RMN de ^1H (500 MHz, $CDCl_3$-d) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3 H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). RMN de ^{19}F (471 MHz, $CDCl_3$-d) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). RMN de ^{13}C (126 MHz, $CDCl_3$-d) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, s ancho), 52.48 (1 C, s ancho), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d, *J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). CL (Cond. OL1): T_R = 1.49 min. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; encontrado: 288.03.

Cap-176

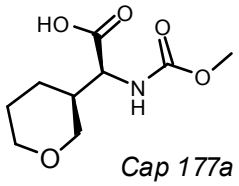


Ácido (S)-2(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético

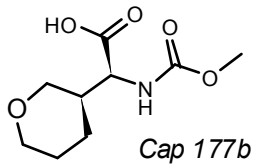
Se añadió una solución de LiOH (0.379 g, 15.83

mmol) en agua (25 ml) a una solución de carbamato Cap-176, etapa f (2.1 g, 7.92 mmol) en THF (75 ml) y la mezcla resultante se agitó a temperatura ambiente durante 4 h. Se eliminó el THF a vacío y la fase acuosa restante se acidificó con solución de HCl 1N (2 ml) y luego se extrajo con EtOAc (2 X 50 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron dando una espuma que correspondía al Cap-176 (1.92 g). RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 12.73 (1 H, s), 7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). RMN de ^{19}F (376 MHz, DMSO-d_6) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). CL (Cond. OL2): T_R = 0.76 min. CL-EM: Análisis calculado para $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; encontrado: 250.10.

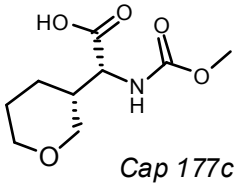
Cap-177a-d



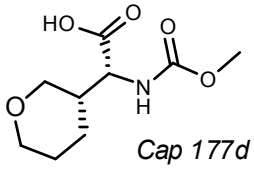
Cap 177a



Cap 177b

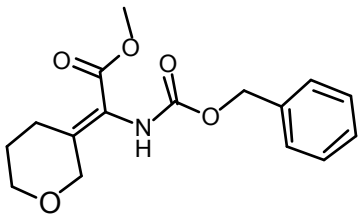


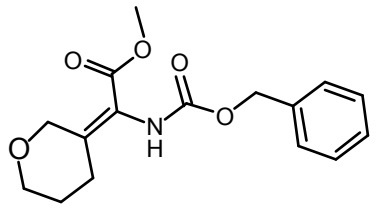
Cap 177c



Cap 177d

Cap-177a-d, etapa a



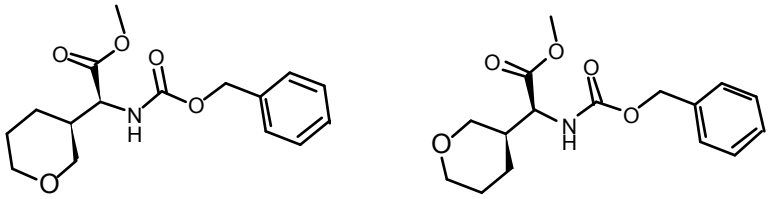


Se añadió 1,1,3,3-tetrametilguanidina (0.985 ml, 7.85 mmol) a una solución agitada de 2-

(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (2.0 g, 6.0 mmol) en EtOAc (40 ml) y la mezcla se agitó a ta bajo N_2 durante 10 min. A continuación se añadió dihidro-2H-piran-3(4H)-ona [23462-75-1] (0.604 g, 6.04 mmol) y la mezcla se agitó a ta durante 16 h. La mezcla de reacción se enfrió entonces en el frigorífico 10 minutos y se neutralizó con ácido cítrico acuoso (1.5 g en 20 ml de agua). Las dos fases se repartieron y la fase orgánica se lavó con HCl acuoso 0.25 N y salmuera, y luego se secó ($MgSO_4$) y se concentró hasta un aceite incoloro. El material bruto se purificó por cromatografía sobre sílice ultrarrápida (disolvente de carga: DCM, eluido con EtOAc/Hexanos, gradiente desde 20% hasta 30% de EtOAc) proporcionando dos productos isoméricos: El primer producto que eluyó fue (Z)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (490 mg) (sólido blanco), y el segundo fue (E)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (433 mg) (sólido blanco). Tiempo de retención de CL-EM 1.398 min (para el isómero Z) y 1.378 min (para el isómero E); m/z 304.08 (para el isómero Z) y 304.16 (para el isómero E) (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución

emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, cloroformo-d) (para el isómero Z) δ ppm 7.30 - 7.44 (m, 5 H), 6.18 (s ancho, 1 H), 5.10 - 5.17 (m, 2 H), 4.22 (s, 2 H), 3.78 (s ancho, 3 H), 2.93 - 3.02 (m, 2 H), 1.80 (dt, *J*=11.7, 5.8 Hz, 2 H), 1.62 (s, 2 H). RMN de ^1H (400 MHz, cloroformo-d) (para el isómero E) δ ppm 7.31 - 7.44 (m, 5 H), 6.12 (s ancho, 1 H), 5.13 - 5.17 (m, 2 H), 4.64 (s ancho, 2 H), 3.70 - 3.82 (m, 5 H), 2.49 (t, *J*=6.5 Hz, 2 H), 1.80 (s ancho, 2 H). (Nota: la regioquímica absoluta se determinó por los desplazamientos de la RMN de ^1H y las constantes de acoplamiento).

Cap-177a-d, etapa b



Se añadió (-)-1,2-bis((2S,5S)-2,5-dimetilfosfolano)etano(ciclooctadieno)-rodio(I)tetrafluoroborato (28.2 mg, 0.051 mmol) a una

solución agitada de (Z)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo (310 mg, 1.015 mmol) en MeOH (10 ml) y la mezcla se aspiró por succión con N_2, seguido por H_2, y a continuación se agitó la reacción bajo H_2 (4.136×10^5 Pa) a ta durante 2d. La mezcla de reacción se concentró y el residuo se purificó por cromatografía sobre sílice ultrarrápida (disolvente de carga: DCM, eluido con EtOAc al 20% en hexanos) proporcionando (S)-2-(benciloxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (204 mg) como un aceite incoloro. Tiempo de retención de CL-EM 1.437 min; m/z 307.89 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, cloroformo-d) δ ppm 7.30 - 7.46 (m, 5 H), 5.32 (d, *J*=8.8 Hz, 1 H), 5.12 (s, 2 H),

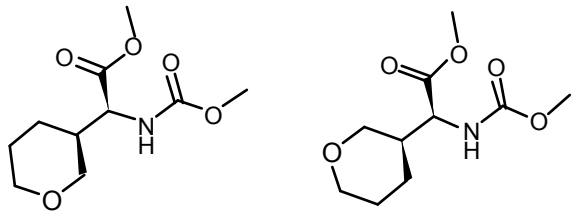
4.36 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.98 (m, 2 H), 3.77 (s, 3 H), 3.28 - 3.37 (m, 1 H), 3.23 (dd, *J*=11.3, 10.5 Hz, 1 H), 2.04 - 2.16 (m, 1 H), 1.61 - 1.75 (m, 3 H), 1.31 - 1.43 (m, 1 H).

El otro estereoisómero ((E)-2-(benciloxicarbonilamino)-2-(2H-piran-3(4H,5H,6H)-iliden)acetato de metilo) (360 mg, 1.18 mmol) se redujo de una forma similar proporcionando (S)-2-(benciloxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo (214 mg) como un aceite incoloro. Tiempo de retención de CL-EM 1.437 min; m/z 308.03 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, CLOROFORMO-d) δ ppm 7.30 - 7.44 (m, 5 H), 5.31 (d, *J*=9.0 Hz, 1 H), 5.12 (s, 2 H),

4.31 (dd, *J*=8.7, 6.9 Hz, 1 H), 3.80 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.37 (td, *J*=10.8, 3.5 Hz, 1 H), 3.28 (dd, *J*=11.3, 9.8 Hz, 1 H), 1.97 - 2.10 (m, 1 H), 1.81 (d, *J*=11.5 Hz, 1 H), 1.61 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

Los enantiómeros individuales de Cap-177a, etapa b (Cap-177c, etapa b) y Cap-177b, etapa b (Cap-177d, etapa b) se prepararon del mismo modo y con rendimientos similares utilizando tetrafluoroborato de (-)-1,2-bis((2R,5R)-2,5-dimetilforfolano)etano(ciclooctadieno)-rodio(I) como catalizador de hidrogenación para las reducciones olefínicas de los materiales de partida estereoisoméricos individuales.

Cap-177a y Cap-177b, etapa c



Se añadió Pd al 10%/C (69.3 mg, 0.065 mmol) a una solución de (S)-2-(benciloxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (200 mg, 0.651 mmol) y dicarbonato de dimetilo [4525-33-1] (0.104 ml, 0.976 mmol) en MeOH (10 ml). La mezcla de reacción se evacuó por succión con N_2, seguido por H_2, y luego se agitó la reacción bajo H_2 (3.79 x 10^5 Pa) a ta durante 5 h. La mezcla de reacción se filtró a través de una almohadilla de CELITE®/sílice y el filtrado se concentró hasta un aceite incoloro. El aceite bruto se purificó por cromatografía sobre sílice ultrarrápida

(disolvente de carga: DCM, eluido con EtOAc al 30% en hexanos) proporcionando el producto (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (132 mg) como aceite incoloro. Tiempo de retención de CL-EM 0.92 min; m/z 231.97 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, cloroformo-d) δ ppm 5.24 (d, *J*=8.5 Hz, 1 H), 4.34 (dd, *J*=8.9, 5.6 Hz, 1 H), 3.84 - 3.97 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.29 - 3.38 (m, 1 H), 3.23 (dd, *J*=11.2, 10.4 Hz, 1 H), 2.03 - 2.14 (m, 1 H), 1.56 - 1.75 (m, 3 H), 1.32 - 1.43 (m, 1 H).

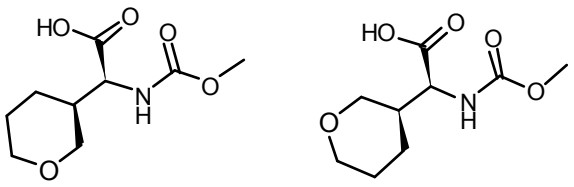
Se transformó el otro diastereómero ((S)-2-(benciloxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo) de una forma similar proporcionando

(S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo como un aceite incoloro. Tiempo de retención de CL-EM 0.99 min; m/z 231.90 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, cloroformo-d) δ ppm 5.25 (d, *J*=8.0 Hz, 1 H), 4.29 (dd, *J*=8.4, 7.2 Hz, 1 H), 3.82 - 3.90 (m, 2 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.37 (td, *J*=10.8, 3.3 Hz, 1 H), 3.28 (t, *J*=10.5 Hz, 1 H), 1.96 - 2.08 (m, 1 H), 1.81 (dd, *J*=12.9, 1.6 Hz, 1 H), 1.56 - 1.72 (m, 2 H), 1.33 - 1.46 (m, 1 H).

Los enantiómeros individuales de Cap-177a, etapa c (Cap-177c, etapa c) y Cap-177b, etapa c (Cap-177d, etapa c) se prepararon del mismo modo y con rendimientos similares usando los materiales de partida apropiados a partir de Cap-

177a-d, etapa b.

Cap-177a y Cap-177b, etapa d



A una solución de (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acetato de metilo (126 mg, 0.545 mmol) en THF (4 ml) agitando a ta se añadió una solución de LiOH 1M (1.090 ml, 1.090 mmol) en agua. La reacción se agitó a ta durante 3h, se neutralizó con HCl 1M (1.1 ml) y se extrajo con EtOAc (3x 10 ml). Los orgánicos se secaron, se filtraron y se concentraron proporcionando ácido (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acético (Cap-177a) (125 mg) como un aceite incoloro transparente. Tiempo de retención de CL-EM 0.44 min; m/z 218.00 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% /

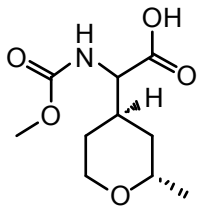
acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^1H (400 MHz, cloroformo-d) δ ppm 5.28 (d, *J*=8.8 Hz, 1 H), 4.38 (dd, *J*=8.7, 5.6 Hz, 1 H), 3.96 - 4.04 (m, 1 H), 3.91 (d, *J*=11.0 Hz, 1 H), 3.71 (s, 3 H), 3.33 - 3.41 (m, 1 H), 3.24 - 3.32 (m, 1 H), 2.10 - 2.24 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.63 - 1.71 (m, 2 H), 1.35 - 1.49 (m, 1 H).

Se transformó otro diastereómero ((S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acetato de metilo) de una forma similar proporcionando ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acético (Cap-177b) como un aceite incoloro. Tiempo de retención de CL-EM 0.41 min; m/z 217.93 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna PHENOMENEX® Luna 10u C18 de 3.0x50mm usando un detector de UV-Vis SPD-10AV a una longitud de onda de detección de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/min, un gradiente de 100% de disolvente A / 0% de disolvente B hasta 0% de disolvente A / 100% de disolvente B, un tiempo de gradiente de 3 minutos, un tiempo de mantenimiento de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era MeOH al 5% / H_2O al 95% / acetato amónico 10 mM y el disolvente B era H_2O al 5% / MeOH

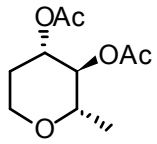
al 95% / acetato amónico 10 mM. Los datos de EM se determinaron usando una Plataforma MICROMASS® para CL en modo electroaspersión. RMN de ^{1}H (400 MHz, cloroformo-d) δ ppm 6.18 (s ancho, 1 H), 5.39 (d, *J*=8.5 Hz, 1 H), 4.27 - 4.37 (m, 1 H), 3.82 - 3.96 (m, 2 H), 3.72 (s, 3 H), 3.42 (td, *J*=10.8, 3.3 Hz, 1 H), 3.35 (t, *J*=10.4 Hz, 1 H), 2.01 - 2.18 (m, 1 H), 1.90 (d, *J*=11.8 Hz, 1 H), 1.59 - 1.76 (m, 2 H), 1.40 - 1.54 (m, 1 H).

Los enantiómeros individuales de Cap-177a (Cap-177c) y Cap-177b (Cap-177d) se prepararon del mismo modo y con rendimientos similares usando los materiales de partida apropiados a partir de Cap-177a-d, etapa c.

Cap-178



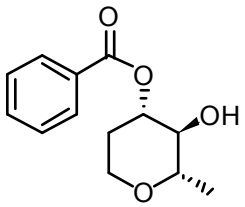
Cap-178, etapa a



A una solución de diacetato de (2S,3S,4S)-2-metil-3,4-dihidro-2H-piran-3,4-diilo (5 g, 23.34 mmol) en 20 ml de MeOH en un depósito de hidrogenación se añadió Pd/C (150 mg, 0.141 mmol). La mezcla resultante se sometió a hidrogenación a 2.757 x 10^5 Pa en un agitador de Parr durante 1 hora. La mezcla se filtró a continuación y el filtrado se concentró

dando Cap-178, etapa a (5.0 g) como un aceite transparente, que solidificó en reposo. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 4.85 - 4.94 (1 H, m), 4.69 (1 H, t, *J*=9.46 Hz), 3.88 - 3.94 (1 H, m), 3.44 (1 H, td, *J*=12.21, 1.83 Hz), 3.36 (1 H, dq, *J*=9.42, 6.12 Hz), 2.03 - 2.08 (1 H, m), 2.02 (3 H, s), 2.00 (3 H, s), 1.70 - 1.80 (1 H, m), 1.16 (3 H, d, *J*=6.10 Hz).

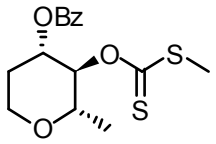
Cap-178, etapa b



A una solución de Cap-178, etapa a (5.0 g, 23 mmol) en 50 ml de MeOH se añadieron varias gotas de metóxido sódico. Después de agitar a temperatura ambiente durante 30 min, se añadió metóxido sódico (0.1 ml, 23.12 mmol) y la solución se agitó a temperatura ambiente durante la noche. El disolvente se eliminó entonces a vacío. El residuo se diluyó con benceno y se concentró dando el diol correspondiente como un sólido amarillo. El sólido se disolvió en 50 ml de piridina y a esta solución a -35°C se añadió cloruro de benzoilo (2.95 ml, 25.4 mmol) gota a gota. La mezcla resultante se agitó a -35 °C durante 1 hora y luego a temperatura ambiente durante la noche. La mezcla se diluyó con Et_2O y se lavó con agua. La fase acuosa se extrajo con EtOAc (2X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por

cromatografía ultrarrápida (gel de sílice, EtOAc al 5%-15%/Hex) dando Cap-178, etapa b (4.5 g) como aceite transparente que cristalizó lentamente tras reposo prolongado. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{13}H_{16}NaO_4$ 259.09; encontrado 259.0; RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8.02 - 8.07 (2 H, m), 7.55 - 7.61 (1 H, m), 7.45 (2 H, t, *J*=7.78 Hz), 5.01 (1 H, ddd, *J*=11.44, 8.70, 5.49 Hz), 3.98 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.54 (1 H, td, *J*=12.36, 2.14 Hz), 3.41 (1 H, t, *J*=9.00 Hz), 3.31 - 3.38 (1 H, m), 2.13 - 2.19 (1 H, m), 1.83 - 1.94 (1 H, m), 1.36 (3 H, d, *J*=5.80 Hz).

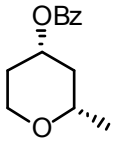
Cap-178, etapa c



A una mezcla de NaH (1.143 g, 28.6 mmol) (60% en aceite mineral) en 6 ml de CS_2 se añadió Cap-178, etapa b (4.5 g, 19 mmol) en 40 ml de CS_2 gota a gota durante 15 min. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La mezcla viró a color naranja claro con algo de sólido. Se añadió gota a gota entonces MeI (14.29 ml, 229 mmol) durante 20 min. La mezcla se agitó entonces a temperatura ambiente durante la noche. La reacción se inactivó cuidadosamente con solución saturada de NH_4Cl. La mezcla se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto

bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 6%/Hex) dando Cap-178, etapa c (3.13 g) como aceite transparente. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{15}H_{18}NaO_4S_2$ 349.05; encontrado 349.11; RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.94 - 8.00 (2 H, m), 7.50 - 7.58 (1 H, m), 7.41 (2 H, t, *J*=7.78 Hz), 5.96 (1 H, t, *J*=9.46 Hz), 5.28 (1 H, ddd, *J*=11.37, 9.38, 5.49 Hz), 4.02 (1 H, ddd, *J*=11.98, 4.96, 1.68 Hz), 3.54 - 3.68 (2 H, m), 2.48 (3 H, s), 2.31 (1 H, dd), 1.88 - 1.99 (1 H, m), 1.28 (3 H, d).

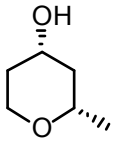
Cap-178, etapa d



A una mezcla de Cap-178, etapa c (3.13 g, 9.59 mmol) y AIBN (120 mg, 0.731 mmol) en 40 ml de benceno a 80 °C se añadió hidruro de tri-n-butilestaño (10.24 ml, 38.4 mmol). La mezcla resultante se agitó a temperatura de reflujo durante 20 min y luego se enfrió hasta temperatura ambiente. La mezcla se diluyó con éter dietílico y se añadieron 100 ml de solución acuosa de KF (10 g) y la mezcla se agitó vigorosamente durante 30 min. Se separaron entonces las dos fases y la fase acuosa se extrajo con EtOAc (2X). La fase orgánica se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, desactivada con Et_3N al 3% en Hexanos y se inyectó Et_3N al 3% en Hexanos para eliminar el derivado de tributilestaño y

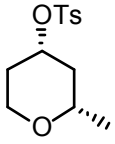
luego se eluyó con EtOAc al 15%/Hex) dando Cap-178, etapa d (1.9 g) como aceite transparente. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7.98 - 8.07 (2 H, m), 7.52 - 7.58 (1 H, m), 7.43 (2 H, t, *J*=7.63 Hz), 5.08 - 5.17 (1 H, m), 4.06 (1 H, ddd, *J*=11.90, 4.88, 1.53 Hz), 3.50 - 3.59 (2 H, m), 2.08 - 2.14 (1 H, m), 1.99 - 2.06 (1 H, m), 1.69 - 1.80 (1 H, m), 1.41 - 1.49 (1 H, m), 1.24 (3 H, d, *J*=6.10 Hz).

Cap-178, etapa e



A una mezcla de Cap-178, etapa d (1.9 g, 8.63 mmol) en 10 ml de MeOH se añadió metóxido sódico (2 ml, 4.00 mmol) (2 M en metanol). La mezcla resultante se agitó a temperatura ambiente durante 5 horas. El disolvente se eliminó a vacío. La mezcla se neutralizó con solución saturada de NH_4Cl y se extrajo con EtOAc (3X). Las fases orgánicas se secaron con $MgSO_4$ y se concentraron dando Cap-178, etapa e (0.8 g) como aceite transparente. El producto se usó en la etapa siguiente sin purificación posterior. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 4.01 (1 H, ddd, *J*=11.80, 5.02, 1.76 Hz), 3.73 - 3.83 (1 H, m), 3.36 - 3.46 (2 H, m), 1.92 - 2.00 (1 H, m), 1.88 (1 H, m), 1.43 - 1.56 (1 H, m), 1.23 (3 H, d), 1.15 - 1.29 (1 H, m).

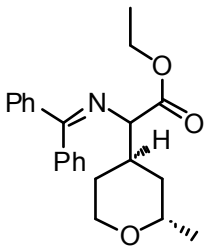
Cap-178, etapa f



Se añadió cloruro de tosilo (2.63 g, 13.77 mmol) a

una solución de Cap-178, etapa e (0.8 g, 6.89 mmol) y piridina (2.23 ml, 27.5 mmol) en 100 ml de CH_2Cl_2. La mezcla resultante se agitó a temperatura ambiente durante 3 días. Se añadieron entonces 10 ml de agua a la mezcla de reacción y la mezcla se agitó a temperatura ambiente durante una hora. Se separaron las dos fases y la fase orgánica se lavó con agua y solución acuosa 1 N de HCl. La fase orgánica se secó con $MgSO_4$ y se concentró dando Cap-178, etapa f (1.75 g) como un sólido amarillo claro. El producto se usó en la etapa siguiente sin purificación posterior. Análisis calculado para $[M+H]^+$ $C_{13}H_{19}O_4S$ 271.10; encontrado 270.90; RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=7.93 Hz), 4.53 - 4.62 (1 H, m), 3.94 (1 H, ddd, *J*=12.13, 4.96, 1.83 Hz), 3.29 - 3.41 (2 H, m), 2.45 (3 H, s), 1.90 - 1.97 (1 H, m), 1.79 - 1.85 (1 H, m), 1.64 - 1.75 (1 H, m), 1.38 - 1.48 (1 H, m), 1.17 (3 H, d, *J*=6.10 Hz).

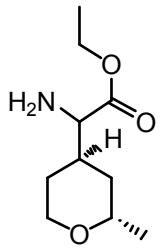
Cap-178, etapa g



En un tubo de microondas se colocó 2-(difenilmetilenamino)acetato de etilo (1.6 g, 5.92 mmol) y Cap-178, etapa f (1.6 g, 5.92 mmol). Se añadieron 10 ml de tolueno. El tubo se selló y se

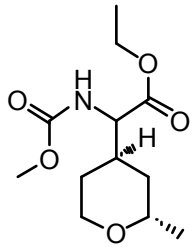
añadió gota a gota bajo N_2 LiHMDS (7.1 ml, 7.10 mmol) (1 N en tolueno). La solución marrón oscura resultante se calentó a 100 °C bajo radiación de microondas durante 6 horas. A la mezcla se añadió entonces agua y la mezcla se extrajo con EtOAc (3X). Las fases orgánicas reunidas se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron dando una mezcla diastereomérica de Cap-3, etapa g (3.1 g) como un aceite naranja. La mezcla bruta se sometió a la etapa siguiente sin separación. CL-EM: Análisis calculado para $[M+H]^+$ $C_{23}H_{28}NO_3$ 366.21; encontrado 366.3.

Cap-178, etapa h



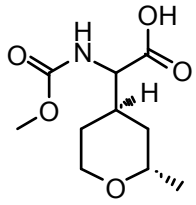
A una solución de la mezcla diastereomérica de Cap-178 de etilo, etapa g en 20 ml de THF se añadió HCl (30 ml, 60.0 mmol) (2 N acuoso). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla se extrajo con EtOAc y la fase acuosa se concentró dando una sal HCl de Cap-178, etapa h (1.9 g) como un aceite naranja. La sal se usó en la etapa siguiente sin purificación posterior. CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{20}NO_3$ 202.14; encontrado 202.1.

Cap-178, etapa i



Se agitó una solución de 1.9 g Cap-178, etapa h (sal HCl), DiPEA (4.19 ml, 24.0 mmol) y cloroformiato de metilo (1.24 ml, 16.0 mmol) en 20 ml de CH_2Cl_2 a temperatura ambiente durante 1 hora. La mezcla se diluyó con CH_2Cl_2 y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-20%/Hex) dando Cap-178, etapa i (1.1 g) como un aceite amarillo. Análisis calculado para $[M+Na]^+$ $C_{12}H_{21}NNaO_5$ 282.13; encontrado 282.14; RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 5.16 (1 H, s ancho), 4.43 - 4.58 (1 H, m), 4.17 - 4.28 (2 H, m), 3.89 - 4.03 (1 H, m), 3.72 - 3.78 (2 H, m), 3.67 - 3.72 (3 H, m), 2.07 - 2.19 (1 H, m), 1.35 - 1.77 (4 H, m), 1.30 (3 H, td, *J*=7.09, 2.89 Hz), 1.19 (3 H, d, *J*=6.53 Hz).

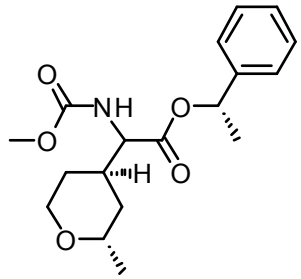
Cap-178, etapa j



A una mezcla de Cap-178, etapa i (1.1 g, 4.2 mmol) en 5 ml de THF y 2 ml de agua se añadió LiOH (6.36 ml, 12.7

mmol) (2 N ac.). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se neutralizó entonces con HCl acuoso 1 N y se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron dando Cap-178, etapa j (0.8 g) como un aceite transparente. CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; encontrado 232.1; RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 5.20 (1 H, d, *J*=8.28 Hz), 4.54 (1 H, t, *J*=8.16 Hz), 3.95 - 4.10 (1 H, m), 3.66 - 3.85 (5 H, m), 2.15 - 2.29 (1 H, m), 1.41 - 1.85 (4 H, m), 1.23 (3 H, dd, *J*=6.53, 1.76 Hz).

Cap-178, etapa k

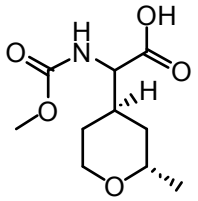


A una solución de Cap-178, etapa j (240 mg, 1.04 mmol), (S)-1-feniletanol (0.141 ml, 1.142 mmol) y EDC (219 mg, 1.14 mmol) en 10 ml de CH_2Cl_2 se añadió DMAP (13.95 mg, 0.114 mmol). La solución resultante se agitó a temperatura ambiente durante la noche y el disolvente se eliminó a vacío. El residuo se recogió en EtOAc, se lavó con agua, se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía (gel de sílice, EtOAc al 0-15%/Hexanos) dando Cap-178, etapa k como una mezcla de dos diastereómeros. La mezcla se separó por HPLC quiral (columna CHIRALPAK® AS, 21 x

250 mm, 10 um) eluyendo con dietilamina al 90% / heptano al 0.1% /EtOH al 10% a 15 ml/min dando Cap-178, estereoisómero 1 de la etapa k (eluye primero) y Cap-178, estereoisómero 2 de la etapa k (eluye segundo) como sólido blancos. La estereoquímica de los dos isómeros no se determinó.

Cap-178, estereoisómero 1 de la etapa k (130 mg): CL-EM: Análisis calculado para $[M+Na]^+$ $C_{18}H_{25}NNaO_5$ 358.16; encontrado 358.16; RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.28 - 7.38 (5 H, m), 5.94 (1 H, q, *J*=6.71 Hz), 5.12 (1 H, d, *J*=9.16 Hz), 4.55 (1 H, t, *J*=9.00 Hz), 3.72 - 3.81 (1 H, m), 3.67 (3 H, s), 3.60 - 3.70 (2 H, m), 1.98 - 2.08 (1 H, m), 1.59 (3 H, d, *J*=6.71 Hz), 1.38 - 1.47 (2 H, m), 1.30 (2 H, t, *J*=5.34 Hz), 0.93 (3 H, d, *J*=6.41 Hz).

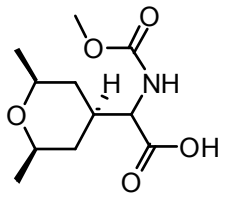
Cap-178, estereoisómero l



A una solución de Cap-178, estereoisómero 1 de la etapa k (ácido (S)-2-(metoxicarbonilamino)-2-((2S,4R)-2-metiltetrahidro-2H-piran-4-il)acético) (150 mg, 0.447 mmol) en 10 ml de EtOH se añadió Pd/C (20 mg, 0.188 mmol) y la mezcla se sometió a hidrogenación en un agitador de Parr a 2.757×10^5 Pa durante la noche. La mezcla se filtró a continuación y el filtrado se concentró dando Cap-178, estereoisómero 1 (100 mg) como un sólido blanco pegajoso. CL-

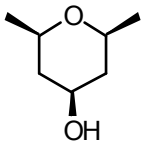
EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; encontrado 232.1; RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.14 - 5.27 (1 H, m), 4.51 (1 H, t, *J*=8.39 Hz), 3.90 - 4.07 (1 H, m), 3.60 - 3.83 (5 H, m), 2.06 - 2.27 (1 H, m), 1.45 - 1.77 (4 H, m), 1.21 (3 H, d, *J*=6.41 Hz).

Cap-179 (Enantiómero-1 y enantiómero-2)



179: estereoisómero 1
179: estereoisómero 2

Cap-179, etapa a



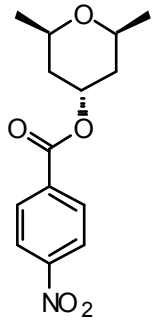
Se disolvió 2,6-dimetil-4H-piran-4-ona (10 g, 81 mmol) en etanol (125 ml) y se añadió Pd/C (1 g, 0.94 mmol). La mezcla se sometió a hidrogenación en un agitador de Parr bajo H_2 (0.325 g, 161 mmol) (4.825 x 10^5 Pa) a temperatura ambiente durante 12 horas. El catalizador se filtró a través de una almohadilla de CELITE® y se lavó con etanol. El filtrado se concentró a vacío y le residuo se purificó por BIOTAGE® (EtOAc 2% a 25 %/Hex; columna de 160 g).Se aislaron dos fracciones de aceites transparentes. La primera que eluye corresponde a (2R,6S)-2,6-dimetildihidro-2H-piran-4(3H)-ona (1.8 g) mientras que la segunda corresponde a Cap-179, etapa a (1.8 g).

Datos de (2R,6S)-2,6-dimetildihidro-2H-piran-4(3H)-

ona: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 3.69 (2 H, ddd, *J*=11.29, 5.95, 2.29 Hz), 2.24 - 2.36 (2 H, m), 2.08 - 2.23 (2 H, m), 1.18 - 1.34 (6 H, m); RMN de ^{13}C (126 MHz, $CDCl_3$) δ ppm 206.96 (1 C, s ancho), 72.69 (2 C, s), 48.70 (2 C, s), 21.72 (2 C, s).

Datos de Cap-179, etapa a: RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 3.69 - 3.78 (1 H, m), 3.36 - 3.47 (2 H, m), 2.10 (1 H, s ancho), 1.88 (2 H, dd, *J*=12.05, 4.73 Hz), 1.19 (6 H, d, *J*=6.10 Hz), 1.10 (2 H, q, *J*=10.70 Hz); RMN de ^{13}C (126 MHz, $CDCl_3$) δ ppm 71.44 (2 C, s), 67.92 (1 C, s), 42.59 (2 C, s), 21.71 (2 C, s).

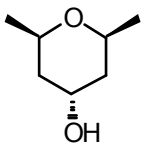
Cap-179, etapa b



Se añadió gota a gota DEAD (2.311 ml, 14.59 mmol) a una solución de Cap-179, etapa a (0.38 g, 2.92 mmol), ácido 4-nitrobenzoico (2.195 g, 13.14 mmol) y Ph_3P (3.83 g, 14.59 mmol) en benceno (25 ml). Se detectó generación de calor y la solución ámbar resultante se agitó a temperatura ambiente durante 6 horas. El disolvente se eliminó a presión reducid y el residuo se purificó mediante BIOTAGE® (EtOAc al 0 a 15%/Hex; columna de 80 g). Se aisló un sólido blanco que

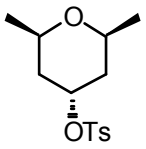
corresponde a Cap-179, etapa b (0.77 g). CL-EM: Análisis calculado para $[M]^+$ $C_{14}H_{17}NO_5$: 279.11; encontrado 279.12. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8.27 - 8.32 (2 H, m), 8.20 - 8.24 (2 H, m), 5.45 (1 H, quin, *J*=2.82 Hz), 3.92 (2 H, dqd, *J*=11.90, 6.10, 6.10, 6.10, 1.53 Hz), 1.91 (2 H, dd, *J*=14.80, 2.29 Hz), 1.57 (3 H, dt, *J*=14.65, 3.05 Hz), 1.22 (6 H, d, *J*=6.10 Hz).

Cap-179, etapa c



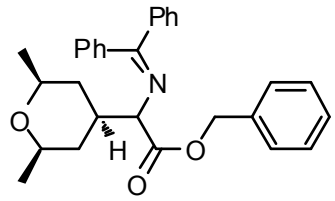
Se añadió una solución de LiOH (0.330 g, 13.8 mmol) en agua (8 ml) a una solución de Cap-179, etapa b (0.77 g, 2.76 mmol) en THF (30 ml) y la mezcla resultante se agitó a temperatura ambiente durante 16 h. Se eliminó el THF a presión reducida y la fase acuosa se diluyó con más agua (20 ml) y se extrajo con EtOAc (3 X 15 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. Se recuperó un residuo oleoso con un sólido blanco. La mezcla se trituró con hexanos y el sólido se separó por filtración proporcionando un aceite transparente que corresponde a Cap-179, etapa c (0.34 g). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4.21 (1 H, quin, *J*=2.82 Hz), 3.87 - 3.95 (2 H, m), 1.72 (1 H, s ancho), 1.63 (2 H, dd, *J*=14.34, 2.14 Hz), 1.39 - 1.47 (2 H, m), 1.17 (6 H, d, *J*=6.41 Hz).

Cap-179, etapa d



Se añadió cloruro de p-tosilo (3.98 g, 20.89 mmol) a una solución de Cap-179, etapa c (1.36 g, 10.5 mmol) y piridina (3.38 ml, 41.8 mmol) en CH_2Cl_2 (150 ml) a temperatura ambiente y se agitó durante 24 horas y luego se concentró hasta un aceite amarillo. El residuo que queda se añadió a piridina (20 ml) y agua (30 ml) y la mezcla resultante se agitó a temperatura ambiente durante 1 1/2 h. La mezcla se extrajo con Et_2O (75 ml) y la fase orgánica separada se lavó concienzudamente con HCl acuoso 1 N (4 X 50 ml). La fase orgánica se secó a continuación ($MgSO_4$), se filtró y se concentró. Se aisló un sólido blanco que corresponde a Cap-179, etapa d (2.2 g). CL-EM: Análisis calculado para $[2M+H]^+$ $C_{28}H_{41}O_8S_2$: 569.22; encontrado 569.3. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.35 (2 H, d, *J*=8.03 Hz), 4.89 (1 H, quin, *J*=2.82 Hz), 3.77 - 3.88 (2 H, m), 2.46 (3 H, s), 1.77 (2 H, dd, *J*=14.93, 2.89 Hz), 1.36 (2 H, ddd, *J*=14.31, 11.54, 2.76 Hz), 1.13 (6 H, d, *J*=6.27 Hz).

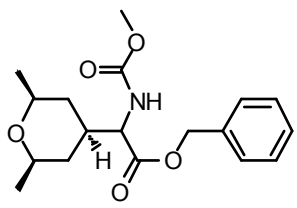
Cap-179, etapa e



Se añadió LiHMDS (4.30 ml, 4.30 mmol) a una

solución de Cap-179, etapa d (1.02 g, 3.59 mmol) y 2-(difenilmetilenamino)acetato de bencilo (1.181 g, 3.59 mmol) en tolueno (25 ml) a temperatura ambiente en un vial de microondas sellado y la mezcla resultante se agitó entonces durante 5 h a 100 °C bajo radiación de microondas. La reacción se inactivó con agua (10 ml), se extrajo con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró y se concentró a vacío. El residuo se purificó por BIOTAGE® (EtOAc al 0% a 6%/Hex; columna de 80 g) y se aisló un aceite amarillo que correspondía a Cap-179, etapa e (1.2 g). Análisis calculado para $[2M+Na]^+$ $C_{58}H_{62}N_2NaO_6$: 905.45; encontrado 905.42. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.70 (4 H, m), 7.29 - 7.44 (29 H, m), 7.06 (4 H, dd, *J*=7.65, 1.63 Hz), 5.18 (2 H, d, *J*=2.01 Hz), 3.89 (2 H, d, *J*=6.53 Hz), 3.79 - 3.87 (1 H, m), 3.46 (5 H, dquind, *J*=11.26, 5.87, 5.87, 5.87, 5.87, 1.88 Hz), 2.47 (2 H, s), 2.35 - 2.46 (2 H, m), 1.78 (1 H, dd, *J*=14.81, 3.01 Hz), 1.62 - 1.65 (1 H, m), 1.61 (2 H, s), 1.36 - 1.43 (3 H, m), 1.19 (7 H, d, *J*=6.27 Hz), 1.14 (11 H, dd, *J*=6.15, 2.89 Hz), 0.86 - 0.96 (3 H, m).

Cap-179, etapa f (enantiómero-1 y enantiómero-2)



Se disolvió Cap-179, etapa e (2.08 g, 4.71 mmol) en THF (100 ml) y se trató con HCl 2 N (9.42 ml, 18.84 mmol). La

solución transparente resultante se agitó a temperatura ambiente durante 4 h y luego se eliminó el THF a presión reducida. La fase acuosa que quedó se extrajo con hexanos (3 X 20 ml) y, después de diluir con H_2O (20 ml), se basificó la fase acuosa con NaOH 1 N hasta pH = 10 y se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo resultante se recogió en CH_2Cl_2 (100 ml) y se cargó con DIEA (2.468 ml, 14.13 mmol) y cloroformiato de metilo (0.401 ml, 5.18 mmol). La solución resultante se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se inactivó con agua (10 ml) y la fase orgánica se eliminó a presión reducida. La fase acuosa se extrajo entonces con EtOAc (3 x 10 ml) y las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por BIOTAGE® (EtOAc al 10%/Hex; columna de 25 g). Se recuperó un aceite incoloro transparente que correspondía a Cap-179, etapa f (1.05 g). CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{26}NO_5$: 336.18; encontrado 336.3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.40 (5 H, m), 5.26 (1 H, d, *J*=8.24 Hz), 5.13 - 5.24 (2 H, m), 4.36 (1 H, dd, *J*=8.85, 4.88 Hz), 3.68 (3 H, s), 3.32 - 3.46 (2 H, m), 2.02 - 2.14 (1 H, m), 1.52 (1 H, d, *J*=12.82 Hz), 1.32 (1 H, d, *J*=12.51 Hz), 1.11 - 1.18 (6 H, m), 0.89 - 1.07 (2 H, m).

Se desarrolló un procedimiento de SFC quiral para

separar la mezcla racémica usando metanol al 12% como modificador en una columna CHIRALPAK® AD-H (30 x 250mm, 5μm) (Temp = 35 °C, Presión = 150 x 10^5 Pa, Longitud de onda = 210 nm, Caudal = 70 ml/min durante 8 min, Disolvente A = CO_2, Disolvente B = MeOH). Los dos isómeros separados , Cap-179 etapa f (enantiómero-1) (eluye primero) y Cap-179 etapa f (enantiómero-2) (eluye segundo) presentaron los mismos datos analíticos que la mezcla correspondiente (véase más arriba).

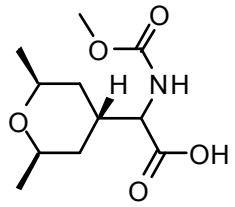
Cap-179 (Enantiómero-1 y enantiómero-2)

Se disolvió Cap-179 etapa f (Enantiómero-1) (0.35 g, 1.044 mmol) en MeOH (50 ml) en un aparato de Parr y se cargó con Pd/C (0.111 g, 1.044 mmol). La suspensión se colocó entonces en un agitador de Parr y se inyectó N_2 (3X) a la mezcla, se colocó bajo 2.757 x 10^5 Pa de H_2 (2.104 mg, 1.044 mmol) y se agitó a temperatura ambiente durante 2 h. El catalizador se separó por filtración a través de una almohadilla de CELITE® y el disolvente se eliminó a presión reducida, proporcionando un sólido ámbar que corresponde a Cap-179 Enantiómero-1 (0.25 g). RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 12.74 (4 H, s ancho), 7.35 (4 H, d, *J*=6.10 Hz), 3.85 (4 H, s ancho), 3.53 (3 H, s), 3.35 (2 H, ddd, *J*=15.95, 9.99, 6.10 Hz), 1.97 (1 H, s ancho), 1.48 (2 H, t, *J*=13.28 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.82 - 1.00 (2 H, m)

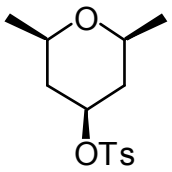
Se preparó Cap-179 Enantiómero-2 de igual forma: RMN de ^{1}H (500 MHz, DMSO-d_6) δ ppm 12.50 (1 H, s ancho), 7.31

(1 H, s ancho), 3.84 (1 H, t, *J*=7.32 Hz), 3.53 (3 H, s), 3.29 - 3.41 (2 H, m), 1.99 (1 H, s), 1.48 (2 H, t, *J*=14.34 Hz), 1.06 (6 H, d, *J*=6.10 Hz), 0.95 (1 H, q, *J*=12.21 Hz), 0.87 (1 H, q, *J*=11.80 Hz). [Nota: la menor variación en el perfil de RMN de ^{1}H de los enantiómeros es probablemente un resultado de una diferencia en la concentración de muestra.]

Cap-180 Mezcla racémica



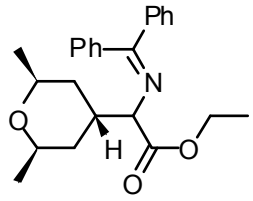
Cap-180, etapa a



Se añadió cloruro de p-tosilo (4.39 g, 23.0 mmol) a una solución de Cap-179, etapa a (1.50 g, 11.5 mmol) y piridina (3.73 ml, 46.1 mmol) en CH_2Cl_2 (50 ml) a temperatura ambiente y se agitó durante 2 días. La reacción se diluyó con CH_2Cl_2, se lavó con agua y luego con HCl 1 N. La fase orgánica se secó ($MgSO_4$) y se concentró hasta un aceite amarillo que se purificó por BIOTAGE® (EtOAc al 5% a 20%/Hex; columna de 40 g). Se aisló un aceite transparente que solidificó a vacío y que corresponde a Cap-180 etapa a (2.89 g). CL-EM: Análisis calculado para $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$: 591.21; encontrado 591.3. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.24 Hz),

7.35 (2 H, d, *J*=7.93 Hz), 4.59 (1 H, tt, *J*=11.37, 4.96 Hz), 3.36 - 3.46 (2 H, m), 2.46 (3 H, s), 1.91 (2 H, dd, *J*=12.05, 5.04 Hz), 1.37 (2 H, dt, *J*=12.67, 11.52 Hz), 1.19 (6 H, d, *J*=6.10 Hz).

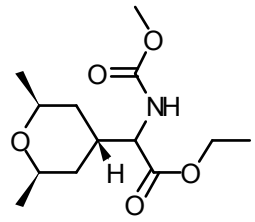
Cap-180, etapa b



Se añadió LiHMDS 1 N (7.09 ml, 7.09 mmol) a una solución de Cap-180, etapa a (1.68 g, 5.91 mmol) y 2-(difenilmetilenamino)acetato de etilo (1.579 g, 5.91 mmol) en tolueno (30 ml) a temperatura ambiente y la mezcla resultante se agitó entonces durante 16 h a 85 °C. La reacción se inactivó con agua (50 ml), se extrajo con EtOAc, se lavó con agua, se secó sobre $MgSO_4$, se filtró y se concentró en vacuo. El residuo se purificó por BIOTAGE® (EtOAc al 0% a 15%/Hex; columna de 40 g). Se aisló un aceite amarillento transparente que corresponde a Cap-180, etapa b (mezcla racémica) (0.64 g). CL-EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{30}NO_3$: 380.22; encontrado 380.03. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7.64 - 7.70 (2 H, m), 7.45 - 7.51 (3 H, m), 7.38 - 7.44 (1 H, m), 7.31 - 7.37 (2 H, m), 7.13 - 7.19 (2 H, m), 4.39 (1 H, d, *J*=10.54 Hz), 4.16 - 4.26 (2 H, m), 3.29 - 3.39 (1 H, m), 2.93 - 3.03 (1 H, m), 2.70 (1 H, m, *J*=9.41, 4.14 Hz), 1.42 - 1.49 (2 H, m), 1.31 - 1.37 (1 H, m), 1.29 (4 H, t, *J*=7.15 Hz),

1.04 (6 H, dd, *J*=7.78, 6.27 Hz).

Cap-180, etapa c



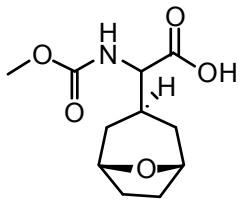
Se disolvió Cap-180, etapa b (0.36 g, 0.949 mmol) en THF (10 ml) y se trató con HCl 2 N (1.897 ml, 3.79 mmol). La solución transparente resultante se agitó a temperatura ambiente durante 20 h y se eliminó el THF a presión reducida. La fase acuosa que quedó se extrajo con hexanos (3 X 20 ml) y, después de diluir con H_2O (20 ml), se basificó la fase acuosa con NaOH 1 N hasta pH = 10 y se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo resultante se recogió en CH_2Cl_2 (10.00 ml) y se cargó con DIEA (0.497 ml, 2.85 mmol) y cloroformiato de metilo (0.081 ml, 1.044 mmol). La solución resultante se agitó a temperatura ambiente durante 2 h y la mezcla de reacción se inactivó con agua (10 ml) y la fase orgánica se eliminó a presión reducida. La fase acuosa se extrajo con EtOAc (3 x 10 ml) y las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron. Se recuperó un sólido ámbar que corresponde a Cap-180, etapa c (0.21 g) y se usó sin purificación posterior. CL-EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{24}NO_5$: 273.17; encontrado 274.06. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 5.20 (1 H, d, *J*=8.03

Hz), 4.59 (1 H, t, *J*=10.16 Hz), 4.11 - 4.27 (3 H, m), 3.69 - 3.82 (2 H, m), 3.64 (3 H, s), 1.95 - 2.07 (1 H, m), 1.63 (1 H, d, *J*=13.80 Hz), 1.41 (2 H, dd, *J*=8.03, 4.02 Hz), 1.31 - 1.37 (1 H, m), 1.26 (3 H, t, *J*=7.15 Hz), 1.16 (1 H, d, *J*=6.27 Hz), 1.12 (6 H, dd, *J*=6.15, 3.89 Hz).

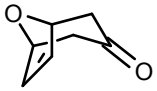
Cap-180 (Mezcla racémica)

Se disolvió Cap-180, etapa c (0.32 g, 1.2 mmol) en THF (10 ml) y se cargó con LiOH (0.056 g, 2.342 mmol) en agua (3.33 ml) a 0 °C. La solución resultante se agitó a ta durante 2 h. Se eliminó el THF a presión reducida y el residuo que quedó se diluyó con agua (15 ml) y se lavó con Et_2O (2 x 10 ml). La fase acuosa se acidificó seguidamente con HCl 1 N hasta pH ~ 2 y se extrajo con EtOAc (3 x 15 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío proporcionando Cap-180 (mezcla racémica) (0.2 g) como una espuma blanca. CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{20}NO_5$: 246.13; encontrado 246.00. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 5.14 (1 H, d, *J*=9.03 Hz), 4.65 (1 H, t, *J*=9.91 Hz), 3.63 - 3.89 (5 H, m), 1.99 - 2.13 (1 H, m), 1.56 - 1.73 (2 H, m), 1.48 - 1.55 (1 H, m), 1.35 - 1.48 (1 H, m), 1.27 (1 H, s ancho), 1.17 (6 H, d, *J*=6.02 Hz).

Cap-185 (Enantiómero-1 y Enantiómero -2)



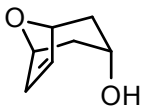
Cap-185, etapa a



A una mezcla de furano (1.075 ml, 14.69 mmol) y zinc (1.585 g, 24.24 mmol) en 1 ml de THF se añadió 1,1,3,3-tetrabromopropan-2-ona (8.23 g, 22.03 mmol) y trietil borato (5.25 ml, 30.8 mmol) en 4 ml de THF gota a gota durante 1 hora en la oscuridad. La mezcla resultante se agitó a temperatura ambiente en la oscuridad durante 17 horas. La mezcla marrón oscuro resultante se enfrió hasta -15 °C, y se añadieron 6 ml de agua. La mezcla se calentó hasta 0 °C y se agitó a esta temperatura durante 30 min. La mezcla se filtró entonces y se lavó con éter. El filtrado se diluyó con agua y se extrajo con éter (3x). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando aceite marrón oscuro. El aceite marrón oscuro se disolvió en 6 ml de MeOH y la solución se añadió gota a gota a una mezcla de zinc (4.99 g, 76 mmol), cloruro de cobre(I) (0.756 g, 7.64 mmol) y cloruro amónico (5.4 g, 101 mmol) en 20 ml de MeOH. La temperatura de reacción se mantuvo por debajo de 15 °C durante la adición. La mezcla se agitó entonces a temperatura ambiente durante 20 horas, se filtró, y el filtrado se diluyó con agua y se extrajo con CH_2Cl_2 (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de

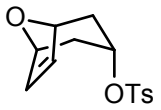
sílice, EtOAc al 0-14%/Hex) proporcionando Cap-185, etapa a como un sólido blanco (1.0 g) como un sólido blanco, que viró rápidamente a amarillo. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 6.24 (2 H, s), 5.01 (2 H, d, *J*=4.88 Hz), 2.73 (2 H, dd, *J*=16.94, 5.04 Hz), 2.31 (2 H, d, *J*=16.79 Hz).

Cap-185, etapa b



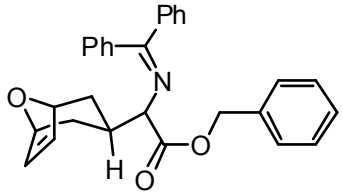
A una solución de Cap-185, etapa a (240 mg, 1.933 mmol) en 2 ml de THF a -78 °C se añadió L-selectrida (3.87 ml, 3.87 mmol) (1 M en THF) gota a gota durante 100 min. La mezcla resultante se agitó a -78 °C durante 1 hora y luego a temperatura ambiente durante la noche. La mezcla se enfrió entonces hasta 0 °C, se añadieron 4 ml de solución acuosa de NaOH al 20%, seguida por 2 ml de H_2O_2 (solución acuosa al 30%) gota a gota. La mezcla resultante se agitó durante 1 hora y luego se neutralizó con HCl 6N (~5 ml). La fase acuosa se saturó con NaCl y se extrajo con CH_2Cl_2 (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-40%/Hex) proporcionando Cap-185, etapa b (180 mg) como aceite transparente. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 6.49 (2 H, s), 4.76 (2 H, d, *J*=4.27 Hz), 3.99 (1 H, t, *J*=5.77 Hz), 2.29 (2 H, ddd, *J*=15.18, 5.65, 4.02 Hz), 1.70 - 1.78 (2 H, m).

Cap-185, etapa c



Se añadió cloruro de p-tosilo (544 mg, 2.85 mmol) a una solución de Cap-185, etapa b (180 mg, 1.427 mmol) y piridina (0.462 ml, 5.71 mmol) en 5 ml de CH_2Cl_2 (5 ml) y la mezcla se agitó a temperatura ambiente durante 2 días. La reacción se diluyó con CH_2Cl_2 y se lavó con HCl acuoso 1 N. La fase acuosa se extrajo con CH_2Cl_2 (2X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-15%/Hex) proporcionando Cap-185, etapa c (210 mg) como un sólido blanco. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.73 (2 H, d, *J*=8.24 Hz), 7.32 (2 H, d, *J*=8.24 Hz), 6.25 (2 H, s), 4.76 (1 H, t, *J*=5.65 Hz), 4.64 (2 H, d, *J*=3.66 Hz), 2.44 (3 H, s), 2.18 (2 H, td, *J*=10.07, 5.49 Hz), 1.71 (2 H, d, *J*=15.56 Hz).

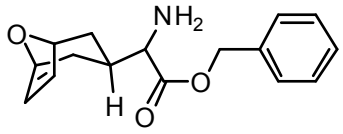
Cap-185, etapa d



Se cargó un tubo de microondas con 2-(difenilmetilenamino)acetato de bencilo (1.5 g, 4.57 mmol) y Cap-185, etapa c (1.28 g, 4.57 mmol) en 5 ml de tolueno. El tubo se selló y se añadió gota a gota bajo N_2 LiHMDS (5.5 ml,

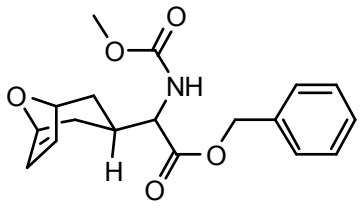
5.5 mmol) (1 N en tolueno). La solución marrón oscura resultante se calentó a 100 °C en microondas durante 5 horas. A la mezcla se añadió entonces agua y EtOAc. Se separaron las fases y la fase acuosa se extrajo con EtOAc (2X). Las fases orgánicas reunidas se concentraron proporcionando Cap-185, etapa d como una mezcla racémica. La mezcla bruta se sometió a la etapa siguiente sin purificación o separación. CL-EM: Análisis calculado para $[M+H]^+$ $C_{29}H_{28}NO_3$ 438.21; encontrado 438.4.

Cap-185, etapa e



A una solución de la mezcla racémica de Cap-185, etapa d en 30 ml de THF se añadió HCl (20 ml) (2 N ac.). La mezcla resultante se agitó a temperatura ambiente durante 2 horas. Después de la reacción se completó como se juzgó por TLC, se separaron las dos capas. La fase acuosa se lavó con EtOAc, se neutralizó con solución acuosa saturada de $NaHCO_3$ y luego se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando Cap-185, etapa e. CL-EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{20}NO_3$ 274.14; encontrado 274.12.

Cap-185, etapa f



Una solución de Cap-185, etapa e bruto, DiPEA (1.24

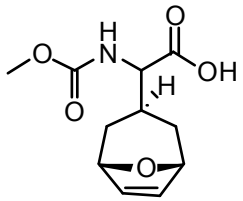
ml, 7.1 mmol) y cloroformiato de metilo (0.55 ml, 7.1 mmol) en 5 ml de CH_2Cl_2 se agitó a temperatura ambiente durante 1 hora. La mezcla se diluyó luego con CH_2Cl_2 y se lavó con agua. La fase orgánica se secó con Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-40%/Hex) proporcionando 700 mg de la mezcla racémica. La mezcla se separó entonces por HPLC quiral (Columna CHIRALPAK® AD-H, 30 x 250 mm, 5 um) eluyendo con CO_2 al 88%-EtOH al 12% a 70 ml/min proporcionando 240 mg de Enantiómero-1 y 310 mg de Enantiómero-2 de Cap-1, etapa f como sólidos blancos. Enantiómero-1: CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; encontrado 332.3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.30 - 7.40 (5 H, m), 6.03 - 6.16 (2 H, m), 5.09 - 5.26 (3 H, m), 4.65 - 4.74 (2 H, m), 4.33 (1 H, dd, *J*=9.16, 4.88 Hz), 3.67 (3 H, s), 2.27 - 2.38 (1 H, m), 1.61 - 1.69 (1 H, m), 1.45 - 1.56 (1 H, m), 1.34 (1 H, dd, *J*=13.43, 5.19 Hz), 1.07 (1 H, dd, *J*=13.12, 5.19 Hz). Enantiómero-2: CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; encontrado 332.06.

Cap-185 (Enantiómero-1 y Enantiómero-2)

A un frasco de hidrogenación que contenía una solución de Cap-185, etapa f (Enantiómero-2) (300 mg, 0.905 mmol) en 10 ml de MeOH se añadió Pd/C (15 mg, 0.141 mmol) bajo una capa de nitrógeno. La mezcla se sometió a hidrogenación en un agitador de Parr a 2.757×10^5 Pa durante

3 horas. La mezcla se filtró entonces y el filtrado se concentró proporcionando Cap-185 (Enantiómero-2) (200 mg) como un sólido blanco. CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{18}NO_5$ 244.12; encontrado 244.2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.33 (1 H, s ancho), 4.46 (2 H, d), 4.28 (1 H, s ancho), 3.68 (3 H, s), 2.35 (1 H, s ancho), 1.91 - 2.03 (2 H, m), 1.56 - 1.80 (4 H, m), 1.36 - 1.55 (2 H, m). [Nota: se puede obtener Cap-185 (Enantiómero-1) de una forma similar.]

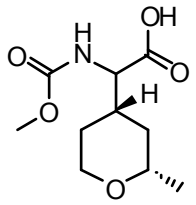
Cap-186



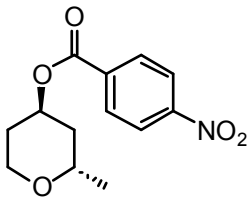
A una solución del éster Cap-185, etapa f (Enantiómero-2) (150 mg, 0.453 mmol) en 4 ml de MeOH se añadió NaOH (4 ml de 1 N en agua, 4.00 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 horas. El metan0ol se eliminó entonces a vacío y el residuo se neutralizó con solución de HCl 1 N y se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando Cap-186 que estaba contaminado con algo de alcohol bencílico (sólido blanco pegajoso; 115 mg). CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_5$ 242.10; encontrado 242.1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 6.10 - 6.19 (2 H, m), 5.36 (1 H, d, *J*=8.85 Hz), 4.75 - 4.84 (2 H, m), 4.28 (1 H, dd, *J*=8.55, 4.58 Hz), 3.68 (3 H, s), 2.33 - 2.45

(1 H, m), 1.60 - 1.72 (2 H, m), 1.30 - 1.48 (2 H, m).

Cap-187

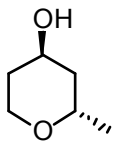


Cap-187, etapa a



A una solución de Cap-178, etapa e (2.2 g, 18.94 mmol), PPh_3 (24.84 g, 95 mmol) y ácido 4-nitrobenzoico (14.24 g, 85 mmol) en 30 ml de benceno se añadió DEAD (42.9 ml, 95 mmol) gota a gota. La solución naranja claro resultante se agitó a temperatura ambiente durante la noche. El disolvente se eliminó entonces a vacío y el residuo se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-15%/Hex) proporcionando Cap-187, etapa a (2.3 g) como un sólido blanco. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8.27 - 8.34 (2 H, m), 8.20 - 8.26 (2 H, m), 5.45 (1 H, t, *J*=2.90 Hz), 3.83 - 3.96 (3 H, m), 1.90 - 2.03 (2 H, m), 1.80 - 1.88 (1 H, m), 1.61 - 1.70 (1 H, m), 1.21 (3 H, d, *J*=6.10 Hz).

Cap-187, etapa b



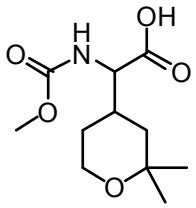
A una solución de Cap-187, etapa a (2.3 g, 8.67 mmol)

en 10 ml de MeOH se añadió metóxido sódico (2.372 ml, 8.67 mmol) (25% en Metanol). La mezcla resultante se agitó a temperatura ambiente durante 3 horas. Se añadió agua y la mezcla se extrajo con EtOAc (5X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-15%/Hex, luego EtOAc al 15-50%/Hex) proporcionando Cap-187, etapa b (0.85 g) como aceite transparente. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4.19 - 4.23 (1 H, m), 3.82 - 3.91 (2 H, m), 3.73 - 3.79 (1 H, m), 1.79 - 1.88 (1 H, m), 1.62 - 1.68 (1 H, m), 1.46 - 1.58 (2 H, m), 1.14 (3 H, d, *J*=6.10 Hz).

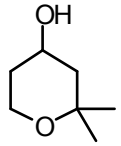
Cap-187

Los enantiómeros individuales de Cap-187 se sintetizaron a partir de Cap-187, etapa b de acuerdo con el procedimiento descrito para Cap-178. CL-EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{18}NO_5$ 232.12; encontrado 232.1. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 5.26 (1 H, d, *J*=7.78 Hz), 4.32 - 4.43 (1 H, m), 4.07 (1 H, dd, *J*=11.54, 3.51 Hz), 3.72 (3 H, s), 3.39 - 3.50 (2 H, m), 2.08 - 2.23 (1 H, m), 1.54 - 1.68 (1 H, m), 1.38 - 1.52 (1 H, m), 1.11 - 1.32 (5 H, m).

Cap-188 (Cuatro estereoisómeros)

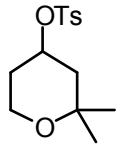


Cap-188, etapa a



A una solución de 2,2-dimetildihidro-2H-piran-4(3H)-ona (2 g, 15.60 mmol) en 50 ml de MeOH se añadió lentamente borohidruro sódico (0.649 g, 17.16 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 horas. A la mezcla se añadió entonces solución acuosa de HCl 1 N hasta que alcanzó el intervalo de pH ácido y luego se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando Cap-188, etapa a (1.9 g) como aceite transparente. El producto se usó en la etapa siguiente sin purificación. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 3.91 - 4.02 (1 H, m), 3.79 - 3.86 (1 H, m), 3.63 (1 H, td, *J*=12.05, 2.51 Hz), 1.82 - 1.93 (2 H, m), 1.40 - 1.53 (1 H, m), 1.29 - 1.38 (1 H, m), 1.27 (3 H, s), 1.20 (3 H, s).

Cap-188.1 y Cap-188.2, etapa b



Se añadió cloruro de p-tosilo (5.56 g, 29.2 mmol) a una solución de Cap-188, etapa a (1.9 g, 14.59 mmol) y piridina (4.72 ml, 58.4 mmol) en 100 ml de CH_2Cl_2. La mezcla resultante se agitó a temperatura ambiente durante 3 días. A la reacción se añadieron 10 ml de agua, y la mezcla se agitó

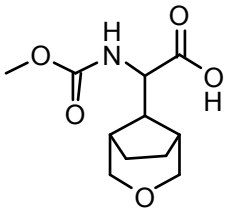
a temperatura ambiente durante una hora más. Se separaron las dos capas y la fase orgánica se lavó con agua y solución acuosa de HCl 1 N. La fase orgánica se secó con $MgSO_4$ y se concentró proporcionando la mezcla de dos enantiómeros como un sólido amarillo claro. La mezcla se separó entonces por HPLC quiral (Columna CHIRALPAK® AD, 21 x 250 mm, 10 um) eluyendo con dietilamina al 92%-heptano al 0.1/EtOH al 8% a 15 ml/min proporcionando Cap-188.1, etapa b (1.0 g) y Cap-188.2, etapa b (1.0 g). La estereoquímica absoluta de los dos enantiómeros no se asignó. Cap-188.1, etapa b: CL-EM: Análisis calculado para $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$ 591.21; encontrado 591.3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.79 (2 H, d, *J*=8.24 Hz), 7.34 (2 H, d, *J*=8.24 Hz), 4.72 - 4.81 (1 H, m), 3.78 (1 H, dt, *J*=12.44, 4.16 Hz), 3.53 - 3.61 (1 H, m), 2.45 (3 H, s), 1.75 - 1.86 (2 H, m), 1.61 - 1.71 (1 H, m), 1.52 - 1.60 (1 H, m), 1.22 (3 H, s), 1.14 (3 H, s). Cap-188.2, etapa b: CL-EM: Análisis calculado para $[2M+Na]^+$ $C_{28}H_{40}NaO_8S_2$ 591.21; encontrado 591.3;

Cap-188

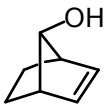
Los cuatro estereoisómeros de Cap-188 se pueden sintetizar a partir de Cap-188.1, etapa b y Cap-188.2, etapa b, de acuerdo con el procedimiento descrito para la preparación de Cap-178. Cap-188 (Estereoisómero-1): CL-EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{19}NNaO_5$ 268.12; encontrado 268.23. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.32 (1 H, d, *J*=8.55

Hz), 4.26 - 4.35 (1 H, m), 3.57 - 3.82 (5 H, m), 2.11 - 2.34 (1 H, m), 1.25 - 1.58 (4 H, m), 1.21 (6 H, d, *J*=6.10 Hz). Cap-188 (Estereoisómero-2): CL-EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{20}NO_5$ 246.13; encontrado 246.1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.25 (1 H, d, *J*=8.55 Hz), 4.33 (1 H, dd, *J*=8.39, 5.04 Hz), 3.80 (1 H, dd, *J*=11.90, 3.97 Hz), 3.62 - 3.76 (4 H, m), 2.20 - 2.32 (1 H, m), 1.52 - 1.63 (1 H, m), 1.27 - 1.49 (3 H, m), 1.22 (6 H, d, *J*=14.04 Hz).

Cap-189



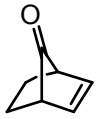
Cap-189, etapa a



A una solución de bromuro de fenilmagnesio (113 ml, 340 mmol) (3 M en éter) en 100 ml de éter se añadió gota a gota exo-2,3-epoxinorbornano (25 g, 227 mmol) en 50 ml de éter. Después de la exotermia inicial, la mezcla se calentó hasta reflujo durante la noche. La reacción se enfrió entonces hasta temperatura ambiente y se inactivó cuidadosamente con agua (~ 10 ml). La mezcla se diluyó con éter y se lavó con una solución acuosa de HCl 3 N (~ 160 ml). La fase acuosa se extrajo con éter (2X) y las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto

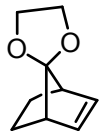
bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-18%/Hex) proporcionando Cap-189, etapa a (11 g). RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 6.03 - 6.11 (2 H, m), 3.76 (1 H, d, *J*=11.29 Hz), 2.72 - 2.81 (2 H, m), 1.98 (1 H, d, *J*=11.29 Hz), 1.67 - 1.76 (2 H, m), 0.90 - 0.97 (2 H, m).

Cap-189, etapa b



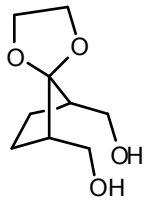
A una solución de cloruro de oxalilo (59.9 ml, 120 mmol) en 200 ml de CH_2Cl_2 a -78 °C se añadió DMSO (17.01 ml, 240 mmol) en 100 ml de CH_2Cl_2. La mezcla se agitó durante 10 min, y se añadió Cap-189, etapa a (11 g, 100 mmol) en 150 ml de CH_2Cl_2 seguido por Et_3N (72.4 ml, 519 mmol) en 30 ml de CH_2Cl_2. La mezcla se agitó a -78 °C durante 30 min y luego se calentó hasta temperatura ambiente. Se añadió agua (150 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Las dos fases se separaron y la fase acuosa se extrajo con CH_2Cl_2 (2X). La fase orgánicas se reunieron, se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-5%/Hex) proporcionando Cap-189, etapa b (5.3 g) como un aceite amarillo claro. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 6.50 - 6.55 (2 H, m), 2.78 - 2.84 (2 H, m), 1.92 - 1.99 (2 H, m), 1.17 - 1.23 (2 H, m).

Cap-189, etapa c



Una mezcla de Cap-189, etapa b (5.3 g, 49.0 mmol), ácido p-toluenosulfónico monohidratado (1.492 g, 7.84 mmol) y etilenglicol (4.10 ml, 73.5 mmol) en 100 ml de benceno se llevó a reflujo durante 4 horas y luego se agitó a temperatura ambiente durante la noche. La reacción se repartió entre Et_2O y solución acuosa saturada de $NaHCO_3$ y se separaron las dos capas. La fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-6%/Hex) proporcionando Cap-189, etapa c (5.2 g) como un aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 6.20 (2 H, t, *J*=2.13 Hz), 3.90 - 3.97 (2 H, m), 3.81 - 3.89 (2 H, m), 2.54 (2 H, m), 1.89 - 1.99 (2 H, m), 0.95 - 1.03 (2 H, m).

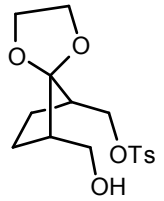
Cap-189, etapa d



Una solución de Cap-189, etapa c (5.2 g, 34.2 mmol) en 60 ml de MeOH y 50 ml de CH_2Cl_2 se enfrió hasta -78 °C y se trató con ozono gas hasta que apareció un color azul claro. La reacción se burbujeó entonces con N_2 para eliminar

el exceso de ozono gas (desapareció el color azul) y se añadió a la reacción borohidruro sódico (1.939 g, 51.3 mmol). La reacción se calentó entonces hasta 0 °C. Se añadió acetona a la mezcla para inactivar el borohidruro sódico en exceso. La mezcla se concentró y el residuo se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 100%) proporcionando Cap-189, etapa d (5.0 g) como un aceite transparente. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 3.99 - 4.09 (4 H, m), 3.68 (4 H, m), 2.17 - 2.29 (2 H, m), 1.92 - 2.10 (2 H, m), 1.77 - 1.88 (2 H, m), 1.57 - 1.70 (2 H, m).

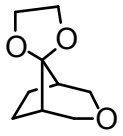
Cap-189, etapa e



A una solución de Cap-189, etapa d (1 g, 5.31 mmol) en 20 ml de CH_2Cl_2 se añadió óxido de plata (3.8 g), cloruro de p-tosilo (1.215 g, 6.38 mmol) y KI (0.176 g, 1.063 mmol). La solución resultante se agitó a temperatura ambiente durante 3 días. La mezcla se filtró entonces y el filtrado se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 60%/Hex) proporcionando Cap-189, etapa e (0.79 g) como aceite transparente. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{16}H_{22}NaO_6S$ 365.10; encontrado 365.22. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 7.80 (2 H, d, *J*=8.28 Hz), 7.36 (2 H, d, *J*=8.03 Hz), 4.11 - 4.17 (1 H, m), 3.85 -

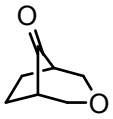
4.06 (5 H, m), 3.64 - 3.71 (1 H, m), 3.55 - 3.63 (1 H, m), 2.47 (3 H, s), 2.32 - 2.43 (1 H, m), 2.15 - 2.27 (1 H, m), 1.70 - 1.89 (2 H, m), 1.52 - 1.66 (1 H, m), 1.35 - 1.47 (1 H, m).

Cap-189, etapa f



A una solución de Cap-189, etapa e (2.2 g, 6.43 mmol) en 40 ml de MeOH se añadió carbonato potásico (1.776 g, 12.85 mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se diluyó luego con agua y EtOAc. Se separaron las dos capas. La fase acuosa se extrajo con EtOAc (2X). Las fases orgánicas reunidas se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-15%/Hex) proporcionando Cap-189, etapa f (0.89 g, 5.23 mmol, 81%) como aceite transparente. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 3.89 - 4.02 (6 H, m), 3.58 (2 H, dd, *J*=10.79, 2.51 Hz), 1.69 - 1.89 (6 H, m).

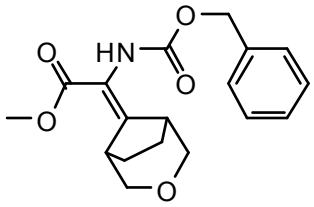
Cap-189, etapa g



A la solución de Cap-189, etapa f (890 mg, 5.23 mmol) en 15 ml de THF se añadió HCl (15 ml, 45.0 mmol) (3 M acuoso). La mezcla resultante se agitó a temperatura ambiente

durante la noche. La mezcla se diluyó luego con éter y se separaron las dos capas. La fase acuosa se extrajo con Éter (2X) y las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando Cap-189, etapa g (0.95 g, que contenía algo de disolventes residuales). El producto se usó en la etapa siguiente sin purificación. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 3.95 - 4.00 (2 H, m), 3.85 (2 H, d, *J*=10.68 Hz), 2.21 - 2.28 (2 H, m), 1.99 - 2.04 (2 H, m), 1.90 - 1.96 (2 H, m).

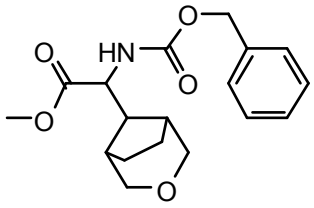
Cap-189, etapa h (Enantiómero-1 y Enantiómero-2)



A una solución de éster trimetílico de (+/-)-benciloxicarbonil-α-fosfonoglicina (1733 mg, 5.23 mmol) en 6 ml de THF a -20 °C se añadió 1,1,3,3-tetrametilguanidina (0.723 ml, 5.75 mmol). La mezcla amarillo claro resultante se agitó a -20 °C durante 1 hora, y se añadió Cap-189, etapa g (660 mg, 5.23 mmol) en 3 ml de THF y la mezcla se agitó entonces a temperatura ambiente durante 3 días. La mezcla de reacción se diluyó luego con EtOAc, se lavó con una solución acuosa 0.1 N de HCl. La fase acuosa se extrajo con EtOAc (2X) y las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-4%/CH_2Cl_2)

proporcionando 960 mg de la mezcla racémica. La mezcla se separó por HPLC quiral (Columna CHIRALPAK® AD, 21 x 250 mm, 10 um) eluyendo con dietilamina al 90%-heptano 0.1% /EtOAc al 10% a 15 ml/min proporcionando Cap-189, etapa h (Enantiómero-1; 300 mg) y Cap-189, etapa h (Enantiómero-2; 310 mg) como sólidos blancos. Cap-189, etapa h (Enantiómero-1): CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; encontrado 332.2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.29 - 7.41 (5 H, m), 6.00 (1 H, s ancho), 5.13 (2 H, s), 3.63 - 3.87 (8 H, m), 2.84 (1 H, s ancho), 1.84 - 2.02 (2 H, m), 1.63 - 1.84 (2 H, m). Cap-189, etapa h (Enantiómero-2): CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{22}NO_5$ 332.15; encontrado 332.2.

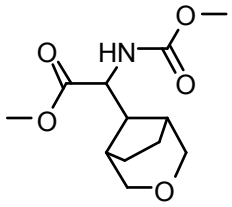
Cap-189, etapa i



Se burbujeó N_2 a través de una solución de Cap-189, etapa h (Enantiómero-2; 290 mg, 0.875 mmol) en 10 ml de MeOH en un frasco de hidrogenación de 500 ml durante 30 minutos. A la solución se añadió (S,S)-Me-BPE-Rh (9.74 mg, 0.018 mmol), y la mezcla se sometió entonces a hidrogenación a 4.136×10^5 Pa durante 6 días. La mezcla se concentró, y la HPLC analítica quiral (columna CHIRALPAK® OJ) indicó que había una pequeña cantidad de material de partida restante y un producto mayoritario. El residuo se separó entonces por HPLC

quiral (Columna CHIRALPAK® OJ, 21 x 250 mm, 10 um) eluyendo con dietilamina al 70%-heptano al 0.1/ EtOAc al 30% a 15 ml/min proporcionando Cap-189, etapa i, (150 mg) como aceite transparente. CL-EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{24}NO_5$ 334.17; encontrado 334.39. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7.28 - 7.41 (5 H, m), 5.12 - 5.18 (1 H, m), 5.09 (2 H, s), 4.05 (1 H, t, *J*=10.07 Hz), 3.75 (3 H, s), 3.60 - 3.72 (2 H, m), 3.41 - 3.50 (2 H, m), 2.10 (1 H, s ancho), 1.72 - 1.99 (6 H, m).

Cap-189, etapa j

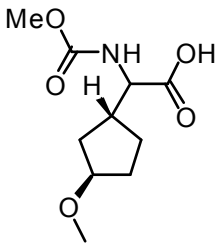


A una solución de Cap-189, etapa i (150 mg, 0.450 mmol) en 10 ml de MeOH en un frasco de hidrogenación se añadieron dicarbonato de dimetilo (0.072 ml, 0.675 mmol) y Pd al 10%/C (23.94 mg, 0.022 mmol) bajo una capa de nitrógeno. La mezcla se sometió entonces a hidrogenación en un agitador de Parr a 3.102 x 10^5 Pa durante la noche. La mezcla se filtró y el filtrado se concentró proporcionando Cap-189, etapa j (110 mg) como un aceite transparente. CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{20}NO_5$ 258.13; encontrado 258.19. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.08 (1 H, d, *J*=9.16 Hz), 4.03 (1 H, t, *J*=10.07 Hz), 3.75 (3 H, s), 3.60 - 3.72 (5 H, m), 3.46 (2 H, t, *J*=10.38 Hz), 2.11 (1 H, s ancho), 1.72 - 1.99 (6 H, m).

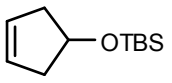
Cap-189

A una mezcla de Cap-189, etapa j (110 mg, 0.428 mmol) en 2 ml de THF y 1 ml de agua se añadió LiOH (0.641 ml, 1.283 mmol) (2 N ac.). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se neutralizó con a solución acuosa de HCl 1 N y se extrajo con EtOAc (3X). Las fases orgánicas reunidas se secaron con $MgSO_4$ y se concentraron proporcionando Cap-189 (100 mg) como un sólido blanco. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{17}NNaO_5$ 266.10; encontrado 266.21. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.10 (1 H, d, *J*=9.16 Hz), 4.02 (1 H, t, *J*=10.07 Hz), 3.62 - 3.78 (5 H, m), 3.49 (2 H, d, *J*=10.68 Hz), 2.07 - 2.22 (2 H, m), 1.72 - 1.98 (6 H, m).

Cap-190 (Mezcla diastereomérica)



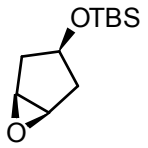
Cap-190, etapa a



A una mezcla de ciclopent-3-enol (2.93 g, 34.8 mmol) e imidazol (5.22 g, 77 mmol) en 30 ml de DMF a 0 °C se añadió t-butildimetilclorosilano (6.30 g, 41.8 mmol). La mezcla incolora resultante se agitó a temperatura ambiente durante la noche. Se añadieron entonces hexanos y agua a la

mezcla y se separaron las dos capas. La fase acuosa se extrajo con EtOAc (2X) y las fases orgánicas reunidas se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 2%/Hex) proporcionando Cap-190, etapa a (6.3 g) como un aceite transparente. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.65 (2 H, s), 4.49 - 4.56 (1 H, m), 2.56 (2 H, dd, *J*=15.26, 7.02 Hz), 2.27 (2 H, dd, *J*=15.26, 3.36 Hz), 0.88 (9 H, s), 0.06 (6 H, s).

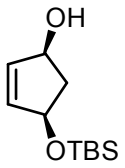
Cap-190, etapa b



A una solución de Cap-190, etapa a (2.3 g, 11.59 mmol) en 40 ml de CH_2Cl_2 a 0 °C se añadió m-CPBA (5.60 g, 16.23 mmol) en 5 porciones. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadieron entonces hexanos y agua a la mezcla y se separaron las dos capas. La fase orgánica se lavó con 50 ml de $NaHSO_3$ al 10% y salmuera, se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 3%-6%/Hex) proporcionando Cap-190, etapa b (1.42 g) y su diastereómero trans (0.53 g) como aceites transparentes. Cap-190, etapa b (cis): RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 4.39 - 4.47 (1 H, m), 3.47 (2 H, s), 2.01 - 2.10 (2 H, m), 1.93 - 2.00 (2 H, m), 0.88 (9 H, s), 0.04 (6 H, s). Cap-190, etapa b

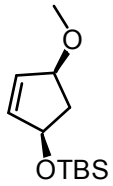
(trans): RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 4.04 - 4.14 (1 H, m), 3.47 (2 H, s), 2.41 (2 H, dd, *J*=14.05, 7.28 Hz), 1.61 (2 H, dd, *J*=14.18, 6.90 Hz), 0.87 (9 H, s), 0.03 (6 H, s).

Cap-190, etapa c



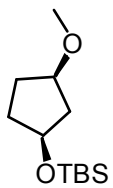
A una solución de (S)-1,2'-metilendipirrolidina (0.831 g, 5.39 mmol) en 15 ml de benceno a 0 °C se añadió gota a gota n-butil litio (4.90 ml, 4.90 mmol) (1 M en hexano). La solución viró a color amarillo brillante. La mezcla se agitó a 0 °C durante 30 min. Se añadió entonces Cap-190, etapa b (cis-isómero; 0.7 g, 3.27 mmol) en 10 ml de benceno y la mezcla resultante se agitó a 0 °C durante 3 horas. Se añadieron EtOAc y solución acuosa saturada de. NH_4Cl a la mezcla, y se separaron las dos capas. La fase orgánica se lavó con agua y salmuera, se secó con $MgSO_4$ y se concentró. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOac al 15%/Hex) proporcionando Cap-190, etapa c (400 mg) como un aceite amarillo claro. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 5.84 - 5.98 (2 H, m), 4.53 - 4.69 (2 H, m), 2.63 - 2.73 (1 H, m), 1.51 (1 H, dt, *J*=13.73, 4.43 Hz), 0.89 (9 H, s), 0.08 (6 H, s).

Cap-190, etapa d



A una solución de Cap-190, etapa c (400 mg, 1.866 mmol), MeI (1.866 ml, 3.73 mmol) (2 M en éter metil t-butílico) en 5 ml de THF a 0 °C se añadió NaH (112 mg, 2.80 mmol) (60% en aceite mineral). La mezcla resultante se dejó calentar hasta temperatura ambiente y se agitó a temperatura ambiente durante la noche. La reacción se inactivó entonces con agua y se extrajo con EtOAc (3X). Las fases orgánicas reunidas se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron. El producto bruto se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 5%/Hex) proporcionando Cap-190, etapa d (370 mg) como aceite amarillo claro. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.92 - 5.96 (1 H, m), 5.87 - 5.91 (1 H, m), 4.64 - 4.69 (1 H, m), 4.23 - 4.28 (1 H, m), 3.32 (3 H, s), 2.62 - 2.69 (1 H, m), 1.54 (1 H, dt, *J*=13.12, 5.49 Hz), 0.89 (9 H, s), 0.07 (5 H, d, *J*=1.83 Hz).

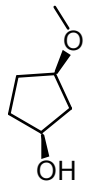
Cap-190, etapa e



A una solución de Cap-190, etapa d (400 mg, 1.751 mmol) en 10 ml de EtOAc en un frasco de hidrogenación se

añadió óxido de platino(IV) (50 mg, 0.220 mmol). La mezcla resultante se sometió a hidrogenación a 3.446 x 10^5 Pa en un agitador de Parr durante 2 horas. La mezcla se filtró entonces a través de CELITE®, y el filtrado se concentró proporcionando Cap-190, etapa e (400 mg) como un aceite transparente. CL-EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{27}O_2Si$ 231.18; encontrado 231.3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4.10 - 4.17 (1 H, m), 3.65 - 3.74 (1 H, m), 3.27 (3 H, s), 1.43 - 1.80 (6 H, m), 0.90 (9 H, s), 0.09 (6 H, s).

Cap-190, etapa f



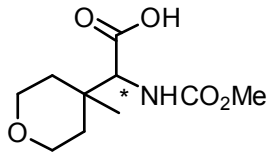
A una solución de Cap-190, etapa e (400 mg, 1.736 mmol) en 5 ml de THF se añadió TBAF (3.65 ml, 3.65 mmol) (1 N en THF). El color de la mezcla viró a marrón después de varios minutos y se agitó a temperatura ambiente durante la noche. El componente volátil se eliminó a vacío y el residuo se purificó por cromatografía ultrarrápida (gel de sílice, EtOAc al 0-25%/Hex) proporcionando Cap-190, etapa f (105 mg) como aceite amarillo claro. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4.25 (1 H, s ancho), 3.84 - 3.92 (1 H, m), 3.29 (3 H, s), 1.67 - 2.02 (6 H, m).

Cap-190

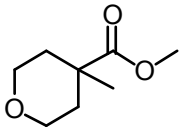
Se sintetizó a continuación Cap-190 a partir de

Cap-190, etapa f de acuerdo con el procedimiento descrito para Cap-182. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{10}H_{17}NNaO_5$ 254.10; encontrado 254.3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 5.25 (1 H, d, *J*=8.55 Hz), 4.27 - 4.41 (1 H, m), 3.81 - 3.90 (1 H, m), 3.69 (3 H, s), 3.26 (3 H, s), 2.46 - 2.58 (1 H, m), 1.76 - 1.99 (3 H, m), 1.64 - 1.73 (1 H, m), 1.40 - 1.58 (1 H, m), 1.22 - 1.38 (1 H, m).

Cap-191 (Enantiómero-1)



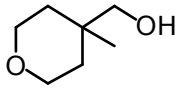
Cap-191, etapa a



A una solución de diisopropilamina (3 ml, 21.05 mmol) en THF (3 ml) a -78 °C bajo hidrógeno se añadió n-butil litio (2.5 M en hexanos; 8.5 ml, 21.25 mmol). La reacción se agitó a -78 °C durante 10 min y luego se llevó hasta 0 °C durante 25 min. La reacción se enfrió de nuevo hasta -78°C, se añadió tetrahidro-2H-piran-4-carboxilato de metilo (3 g, 20.81 mmol) en THF (3 ml). La reacción se agitó a -78 °C durante 15 min y luego se llevó hasta 0 °C durante 30 min. La reacción se enfrió hasta -78 °C, se añadió yoduro de metilo (1.301 ml, 20.81 mmol). Después de la adición, se retiró del baño frío y se dejó que la reacción se calentara lentamente hasta ~25 °C y se agitó durante 22h. Se añadieron acetato de

etilo y HCl acuoso (0.1N), y la fase orgánica se separó y se lavó con salmuera y se secó ($MgSO_4$), se filtró y se concentró a vacío. El residuo se cargó en un cartucho de gel de sílice Thomson eluyendo con acetato de etilo al 10%/hexanos proporcionando un aceite amarillo claro (2.83 g). RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 3.73-3.66 (m, 2H), 3.66 (s, 3H), 3.40-3,30 (m, 2H), 1.95-1.93 (dm, 1H), 1.92-1.90 (dm, 1H), 1.43 (ddd, J = 13.74, 9.72, 3.89, 2H), 1.18 (s, 3H).

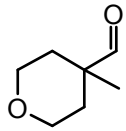
Cap-191, etapa b



A una solución de Cap-191, etapa a (3 g, 18.96 mmol) en tolueno (190 ml) a -78°C bajo nitrógeno se añadió hidruro de diisopropilaluminio (1.5M en tolueno; 26.5 ml, 39.8 mmol) gota a gota. La reacción se continuó agitando a -78 °C durante 1.5h., y se retiró el baño y se agitó durante 18h. La reacción se inactivó con MeOH (20 ml). Se añadió HCl (1M, 150 ml) y la mezcla se extrajo con EtOAc (4 x 40 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo se purificó con cromatografía ultrarrápida (gel de sílice; acetato de etilo al 40%/hexanos) proporcionando un aceite incoloro (1.36 g). RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 3.77 (dt, J = 11.73, 4.55, 2H), 3.69-3.60 (m, 2H), 3.42 (s, 2H), 1.71-1.40 (s ancho, 1H)1.59 (ddd, J = 13.74, 9.72, 4.39,

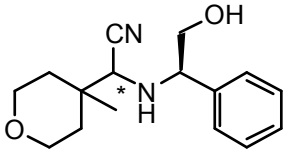
2H), 1.35-1,31 (m, 1H), 1.31-1,27 (m, 1H), 1.06 (s, 3H).

Cap-191, etapa c



A una solución de DMSO (5.9 ml, 83 mmol) en CH_2Cl_2 (85 ml) a -78 °C bajo nitrógeno se añadió cloruro de oxalilo (3.8 ml, 43.4 mmol) y se agitó durante 40 min. Se añadió entonces una solución de Cap-191, etapa b (4.25 g, 32.6 mmol) en CH_2Cl_2 (42.5 ml). La reacción se continuó agitando a -78 °C bajo nitrógeno durante 2h. La reacción se inactivó con K_2HPO_4 frío al 20% (ac) (10 ml) y agua. La mezcla se agitó a ~25 °C durante 15 min, se diluyó con éter dietílico (50 ml) y se separaron las fases. La fase acuosa se extrajo con éter dietílico (2 x 50 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo se recogió en CH_2Cl_2 (4 ml) y se purificó por cromatografía ultrarrápida (gel de sílice, eluyendo con CH_2Cl_2) proporcionando un aceite incoloro (2.1 g). RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 9.49 (s. 1H), 3.80 (dt, J = 11.98.4.67, 2H), 3.53 (ddd, J = 12.05, 9.41, 2.89, 2H), 1.98 (ddd, J = 4.71, 3.20, 1.38, 1H), 1.94 (ddd, *J*= 4.71, 3.20, 1.38, 1H), 1.53 (ddd, J = 13.87, 9.60, 4.14, 2H), 1.12 (s, 3H).

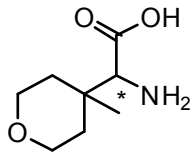
Cap-191, etapa d



A una solución de Cap-191c (2.5 g, 19.51 mmol) en $CHCl_3$ (20 ml) bajo nitrógeno a ~25 °C se añadió (R)-2-amino-2-feniletanol (2.94 g, 21.46 mmol) y se agitó durante 5h. La reacción se enfrió hasta 0 °C, se añadió gota a gota cianuro de trimetilsililo (3.8 ml, 30.4 mmol). El baño frío se retiró y se dejó agitando la reacción a ~25 °C bajo nitrógeno durante 15.5 h. La reacción se trató con HCl 3N (20 ml) y agua (20 ml), y el producto se extrajo con $CHCl_3$ (3 x 50 ml). Las fases orgánicas reunidas se secaron ($NaSO_4$), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida (gel de sílice; acetato de etilo al 40%/hexanos) proporcionando dos diastereómeros: Cap-191, etapa d1 (diastereómero 1) como un aceite incoloro que solidificó en un sólido blanco en reposo (3 g). RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 7.42-7.26 (m, 5H), 5.21 (t, J = 5.77, 1H), 3.87 (dd, J = 8.53, 4.52, 1H), 3.61-3.53 (m, 1H), 3.53-3,37 (m, 5H), 3.10 (d, J = 13.05, 1H), 2.65 (d, J = 13.05, 1H), 1.64-1.55 (m, 1H), 1.55-1.46 (m,1H), 1.46-1,39 (m, 1H), 1.31-1,23 (m, 1H), 1.11 (s, 3H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{23}N_2O_2$: 275.18; encontrado 275.20. Cap-191, etapa d2 (diastereómero 2) como un aceite amarillo

claro (0.5 g). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 7.44-7.21 (m, 5H), 4.82 (t, J = 5.40, 1H), 3.82-3.73 (m, 1H), 3.73-3.61 (m, 3H), 3.61-3,37 (m, 5H), 2.71 (dd, J = 9.29, 4.77, 1H), 1.72-1.55 (m, 2H), 1.48-1,37 (m, 1H), 1.35-1,25 (m, 1H), 1.10 (s, 3H). CL-EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{23}N_2O_2$: 275.18; encontrado 275.20.

Cap-191, etapa e



A una solución de Cap-191, etapa d2 (diastereómero 2) (0.4472 g, 1.630 mmol) en CH_2Cl_2 (11 ml) y MeOH (5.50 ml) a 0 °C bajo nitrógeno se añadió tetraacetato de plomo (1.445 g, 3.26 mmol). La reacción se agitó durante 1.5h, se retiró el baño frío y se continuó agitando durante 20h. La reacción se trató con un regulador de pH fosfato (pH = 7; 6 ml) y se agitó durante 45 min. La reacción se filtró sobre CELITE®, se lavó con CH_2Cl_2 y se separaron las fases. La fase acuosa se extrajo con CH_2Cl_2 (3 X 25 ml), y las fases orgánicas reunidas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida (gel de sílice; acetato de etilo al 15%/hexanos) proporcionando la imina intermedio como un aceite incoloro (181.2 mg). RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 8.55 (d, J = 1.00, 1H), 7.89-7.81 (m, 2H), 7.61-7.46 (m,

3H), 4.80 (d, J = 1.00, 1H), 3.74 (tt, J = 11.80, 4.02, 2H), 3.62-3.46 (m, 2H), 1.79-1.62 (m, 2H), 1.46-1,30 (m, 2H), 1.15 (s, 3H).

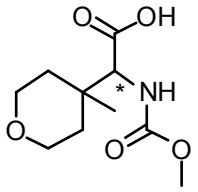
La imina intermedia se recogió en HCl 6N (10 ml) y se calentó a 90 °C durante 10 días. La reacción se retiró del calor, se dejó enfriar hasta temperatura ambiente y se extrajo con acetato de etilo (3 x 25 ml). La fase acuosa se concentró a vacío proporcionando un sólido blanquecino. El sólido se recogió en MeOH y se cargó en un cartucho MCX (6 g) previamente acondicionado, se lavó con MeOH seguido por elución con solución de NH_3 2N/MeOH y se concentró a vacío proporcionando un sólido blanquecino (79.8 mg). RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 14.33-13.51 (s ancho, 1H), 8.30 (s ancho, 3H), 3.82-3.75 (m, 1H), 3.70 (dt, J = 11.80, 4.02, 2H), 3.58-3.43 (m, 2H), 1.76-1.60 (m, 2H), 1.47-1,36 (m, 1H), 1.36-1,27 (m, 1H), 1.08 (s, 3H). CL-EM: Análisis calculado para $[M+H]^+$ $C_8H_{16}NO_3$: 174.11; encontrado 174.19.

Cap-191 (Enantiómero-1)

A una solución de Cap-191, etapa e (0.0669 g, 0.386 mmol) y carbonato sódico (0.020 g, 0.193 mmol) en hidróxido sódico (1M ac.; 0.4 ml, 0.40 mmol) a 0 °C se añadió cloroformiato de metilo (0.035 ml, 0.453 mmol) gota a gota. La reacción se retiró del baño de enfriamiento y se dejó agitar ~25 °C durante 3h. La reacción se lavó con éter dietílico (3 x 20 ml). La fase acuosa se acidificó con HCl

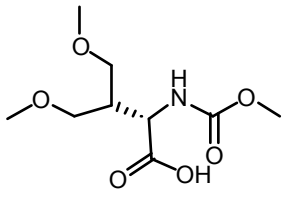
12 N (pH ~ 1-2), y se extrajo con acetato de etilo (2 x 20 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío proporcionando Cap-191 como una película incolora (66.8 mg). RMN de ^1H (400 MHz, DMSO-d_6) δ ppm 13.10-12.37 (s ancho, 1H), 7.37 (d, J = 9.04, 1H), 4.02 (d, J = 9.29, 1H), 3.72-3.57 (m, 2H), 3.56 (s, 3H), 3.54-3.44 (m, 2H), 1.65 (ddd, J = 13.61, 9.72, 4.27, 1H), 1.53 (ddd, J = 13.68, 9.66, 4.27, 1H), 1.41-1,31 (m, 1H), 1.31-1,22 (m, 1H), 1.00 (s, 3H). CL-EM: Análisis calculado para $[M+Na]^+$ $C_{10}H_{17}NO_5Na$: 254.10; encontrado 254.11.

Cap-192 (Enantiómero-2)

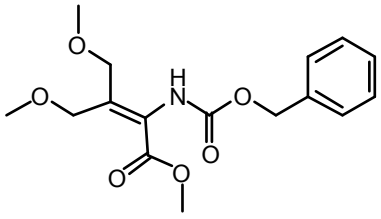


Se preparó Cap-192 (Enantiómero-2) a partir de Cap-191, etapa d1 de acuerdo con el procedimiento descrito para la preparación de su Enantiómero Cap-191.

Cap-193



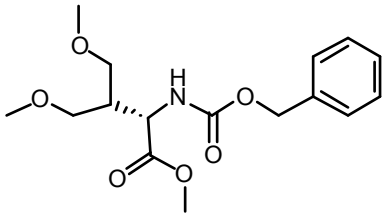
Cap-193, etapa a



A una solución de 2-(benciloxicarbonilamino)-2-

(dimetoxifosforil)acetato de metilo (1.45 g, 4.2 mmol) en DCM se añadió DBU (0.70 ml, 4.7 mmol). La mezlca de reacción se agitó durante 10 minutos, seguido por la adición de una solución de 1,3-dimetoxipropan-2-ona (0.5 g, 4.2 mmol) en DCM. La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se cargó en un cartucho de gel de sílice de 80 g que se eluyó con un gradiente de 18 minutos de EtOAc al 0-70% en hexano proporcionando Cap-193, Etapa a (0.8 g) como un aceite denso. RMN de ^{1}H (400 MHz, MeOD) δ ppm 7.23 - 7.43 (5 H, m), 4.99 - 5.18 (2 H, m), 4.16 (2 H, s), 4.06 (2 H, s), 3.66 - 3.78 (3 H, s), 3.26 (3 H, s), 3.23 (3 H, s). CL/EM: Análisis calculado para $[M+Na]^+$ $C_{16}H_{21}NNaO_6$: 346.14; encontrado: 346.12.

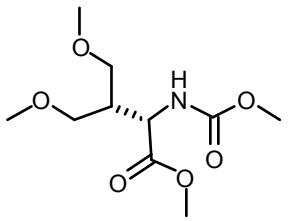
Cap-193, etapa b



Se agitó bajo 3.79 x 10^5 Pa de H_2 durante 18 horas una mezcla del éster Cap-193, Etapa a (0.5 g) y tetrafluoroborato de (+)-1,2-bis((2S,5S)-2,5-dietilfosfolano)benceno(ciclooctadieno)rodio (I) (0.1 g) en MeOH. La mezcla de reacción se concentró hasta sequedad. El residuo se cargó en un cartucho de gel de sílice de 25 g y eluyó con un gradiente de 18 minutos de EtOAc al 0-80% en hexano proporcionando Cap-193, Etapa b (0.49 g) como un

aceite transparente. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{16}H_{23}NNaO_6$: 348.15; encontrado: 348.19.

Cap-193, Etapa c



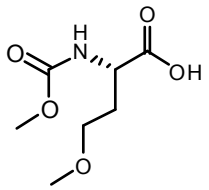
Se agitó bajo H_2 a temperatura ambiente durante 2 horas una mezcla de reacció de Cap-193, Etapa b (0.16 g), carbonato de dimetilo (0.13 g) y Pd al 10%/C (0.026 g) en EtOAc. La mezcla de reacción se filtró y se concentró proporcinando carbamato de metilo Cap-193, Etapa c. CL-EM: Análisis calculado para $[M+Na]^+$ $C_{10}H_{19}NNaO_6$: 272.12; encontrado: 272.07.

Cap-193

A una solución del éster Cap-193, Etapa c en THF (1 ml) y MeOH (0.25 mL) se añadió NaOH 1 N (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró y se diluyó con EtOAc y HCl 1 N. La fase acuosa se extrajo con EtOAc, y la fase orgánica reunida se lavó con NaCl saturada, se secó sobre Na_2SO_4 anhidro, se filtró y se concentró proporcionando Cap-193 (0.082 g). RMN de ^1H (400 MHz, $CDCl_3$) 5.99 (1 H, d, *J*=8.56 Hz), 4.57 (1 H, dd, *J*=8.56, 3.27 Hz), 3.67 (3 H, s), 3.49 (2 H, d, *J*=4.28 Hz), 3.45 - 3.44 (2 H, m), 3.26 - 3.35 (6 H, m). CL-EM: Análisis calculado para $[M+Na]^+$ $C_9H_{17}NNaO_6$: 258.11;

encontrado: 258.13.

Cap-194



Se añadió piperidina (1.0 ml, 10 mmol) a una solución de ácido (S)-2-(((9H-fluoren-9-il)metoxi)carbonilamino)-4-metoxibutanoico (0.355 g, 1 mmol) en DMF (3 ml), y la mezcla se agitó a ta durante 3 horas. Se eliminaron los volátiles y el residuo se repartió entre $NaHCO_3$ saturado (acuoso) (5 ml) y EtOAc (5 ml). La fase acuosa se lavó seguidamente con EtOAc y Et_2O. Se añadió a la solución acuosa Na_2CO_3 (212 mg, 2.0 mmol) seguido por cloroformiato de metilo (0.16 ml, 2.0 mmol) y la mezcla de reacción se agitó durante 16 horas a ta. La mezcla de reacción se acidificó con HCl 1 N (ac.) hasta pH <7 y luego se extrajo con EtOAc (2 x 10 ml). Las fases orgánicas reunidas se secaron (Na_2SO_4), se filtraron y concentraron. El residuo se purificó por cromatografía sobre sílice ultrarrápida (EtOAc/hexanos, gradiente desde 20% a 70%) proporcinando ácido (S)-4-metoxi-2-(metoxicarbonilamino)butanoico (Cap-194) (91.5 mg) como aceite viscoso. Tiempo de retención de CL-EM = 0.61 min; m/z 214 $[M+Na]^+$. (Columna: Phenonenex-Luna 3.0 x 50mm S10. Disolvente A = 90% de agua:10% de metanol: 0.1% de TFA. Disolvente B = 10% de agua :90% de metanol: 0.1% de TFA. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min.

Longitud de onda = 220). RMN de ^{1}H (400 MHz, cloroformo-d) δ ppm 7.41 (s ancho, 1 H), 5.74 - 6.02 (m, 1 H), 4.32 - 4.56 (m, 1 H), 3.70 (s, 3 H), 3.54 (t, *J*=5.0 Hz, 2 H), 3.34 (s, 3 H), 1.99 - 2.23 (m, 2 H).

Sección de Ejemplos

El análisis de masas de baja resolución se realizó en un sistema Shimadzu LC acoplada con un sistema Waters Micromass ZQ MS (*Cond. 1*) o Waters Acquity HPLC con detección Waters PDA UV-Vis y Waters ZQ MS (*Cond. 2*). El tiempo de retención (T_a) se obtuvo empleando las condiciones siguientes y debe destacarse que los tiempos de retención pueden variar ligeramente entre instrumentos:

Condición 1a

Columna = Phenomenex-Luna 4.6 X 30 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de metanol/90% de H_2O

Condición 1b

Columna = Waters Acquity BEH C18; 1.7 μm ; 150 X 2.1 mm ID; (a 35°C)

Conservación 10% de B 0-1 min

10-50% de B 0-25 min

50-98% de B 25-33 min

Conservación 98% de B 32-35 min

98-10% de B 35.0-35.5 min

Conservación 10% de B 35.5-40 min

Caudal = 0.35 ml/min

Longitud de onda = 254 nm

Disolvente A: = 0.05% de TFA en agua

Disolvente B: = 0.05% de TFA en CH_3CN

Condición 1c

Columna = Waters Acquity BEH C18; 1, μm ; 150 X 2.1 mm ID; (a 35 °C)

Conservación 10% de B 0-1min

10-60% de B 1-4 min

60-98% de B 4-21 min

Conservación 98% de B 21-21.5 min

98-10% de B 21.5-22 min

Conservación 10% de B 22-25 min

Caudal = 0.35 ml/min

Longitud de onda = 315 nm

Disolvente A: = 0.05% de TFA en agua

Disolvente B:= 0.05% de TFA en CH_3CN

Condición 2a

Columna = Waters Sunfire C18, 4.6 X 150 mm, 3.5 μm

% inicial de B = 10

% final de B = 50

Tiempo de gradiente = 20 min

Tiempo de detención = varía de 25 a 40 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0.1% de TFA en 5% de CH_3CN/95% de H_2O

Disolvente B: = 0.1% de TFA en 95% de CH_3CN/95% de H_2O

Condición 2b

Columna = Waters Xbridge fenilo, 4.6 X 150 mm, 3 μm

% inicial de B = 10

% final de B = 50

Tiempo de gradiente = 20 min

Tiempo de detención = varía de 25 a 40 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0.1% de TFA en 5% de CH_3CN/95% de H_2O

Disolvente B: = 0.1% de TFA en 95% de CH_3CN/95% de H_2O

Condición 3

Columna = Phenomenex Luna C18 (2), 3 u, 150 x 4.6mm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 10 min

Caudal= 1 ml/min

Longitud de onda= 220 y 256 nm

Disolvente A= H_2O/CH_3CN (95:5) + 0.05% de TFA

Disolvente B= H_2O/CH_3CN (5:95) + 0.05% de TFA

Condición OL1

Columna = Phenomenex-Luna 3.0 X 50 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de detención = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A: = 0.1% de TFA en 10% de metanol/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de metanol/90% de H_2O

Condición OL2

Columna = Phenomenex-Luna 50X 2 mm 3 u

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de detención = 5 min

Caudal = 0.8 ml/min

Temp. del horno = 40 °C

Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de acetonitrilo/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de acetonitrilo/10% de H_2O

Condición OL3

Columna = Waters Acquity BEH C18; 1.7 μm ; 150 X 2.1 mm ID; (a 35 °C)

Conservación 10% de B 0-1min

10-60% de B 1-4 min

60-98% de B 4-21 min

Conservación 98% de B 21-21.5 min

98-10% de B 21.5-22 min

Conservación 10% de B 22-25 min

Caudal = 0.35 ml/min

Longitud de onda = 315 nm

Disolvente A = 0.05% de TFA en agua

Disolvente B = 0.05% de TFA en CH_3CN

Condición OL4a

Columna = Waters Sunfire C18, 4.6 X 150 mm, 3.5 μm

% inicial de B = 10

% final de B = 100

Tiempo de gradiente = 15 min

Tiempo de detención = 18 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0.1% de TFA en 5% de CH_3CN/95% de H_2O

Disolvente B = 0.1% de TFA en 95% de CH_3CN/95% de H_2O

Condición OL4b

Columna = Waters Xbridge fenilo, 4.6 X 150 mm, 3 μm

% inicial de B = 10

% final de B = 50

Tiempo de gradiente = 15 min

Tiempo de detención = 18 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0.1% de TFA en 5% de CH_3CN/95% de H_2O

Disolvente B = 0.1% de TFA en 95% de CH_3CN/95% de H_2O

Condición OL4c

Columna = Waters Aquity BEH C18; 1.7 μm; 50 X 2.1 mm D.I.; (a 35°C)

Conservación 2% de B 0-1 min

2-98% de B 1-1.5 min

98% de B 1.5-2,2 min

Caudal = 0.8 ml/min

Longitud de onda = 2 nm

Disolvente A = 0.05% de TFA en agua

Disolvente B = 0.05% de TFA en CH_3CN

Condición OL5a

Columna = Phenomenex-Luna 3.0 X 50 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de CH_3CN/10% de H_2O

Condición OL5b

Columna = Phenomenex-Luna 3.0 X 50 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = NH_4OAc 10 mM en 5% de metanol/95% de H_2O

Disolvente B = NH_4OAc 10 mM en 95% de CH_3CN/5% de H_2O

Condición D4

Columna = Phenomenex-Luna 3.0 X 50 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de detención = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de metanol/90% de H_2O

Condición J4

Columna = Phenomenex-Luna 4.6 X 50 mm S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de detención = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Disolvente B = 0.1% de TFA en 90% de metanol/90% de H_2O

Condición PY1

Columna = PHENOMENEX 2.0 x 50 mm, 3 µm

% inicial de B = 0; % final de B = 100

Tiempo de gradiente = 4 min; Tiempo de detención =

5 min

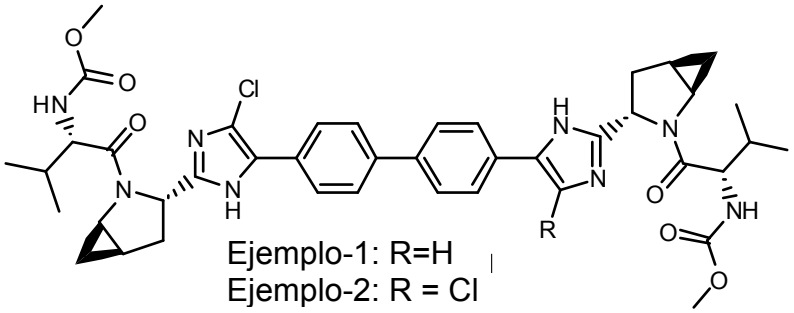
Caudal = 4 ml/min; Longitud de onda = 220 nm

Disolvente A = 0.1% de TFA en 10% de metanol/90% de agua

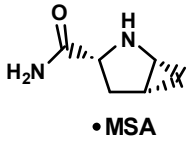
Disolvente B = 0.1% de TFA en 90% de CH_3CN/10% de agua

Temperatura del horno = 40°C

Ejemplos 1 y 2

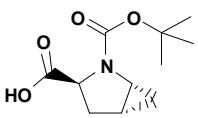


Ejemplo 1, Etapa a



La amida 1a (CH_3SO_3H) se preparó de acuerdo con el procedimiento descrito para la síntesis de su enantiómero en la patente WO2004/052850.

Ejemplo 1, Etapa b

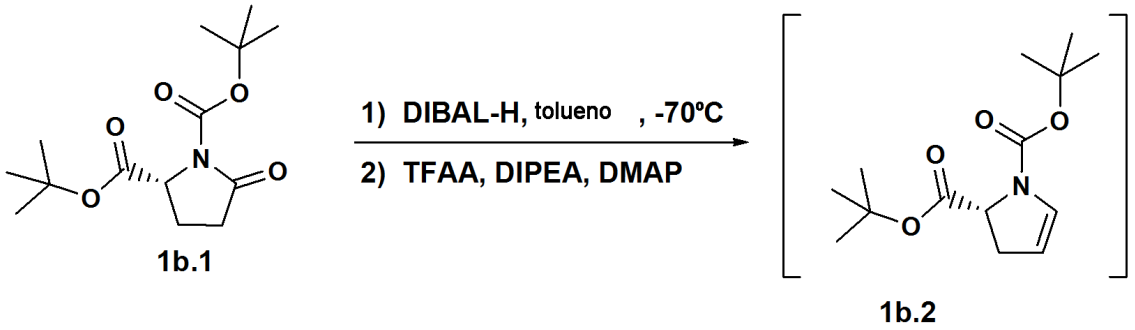


Un matraz de fondo redondo de 1 l equipado con una entrada para nitrógeno, un agitador aéreo, un termoacoplador y un manto de calentamiento se cargó con 50 g (225 mmol) de

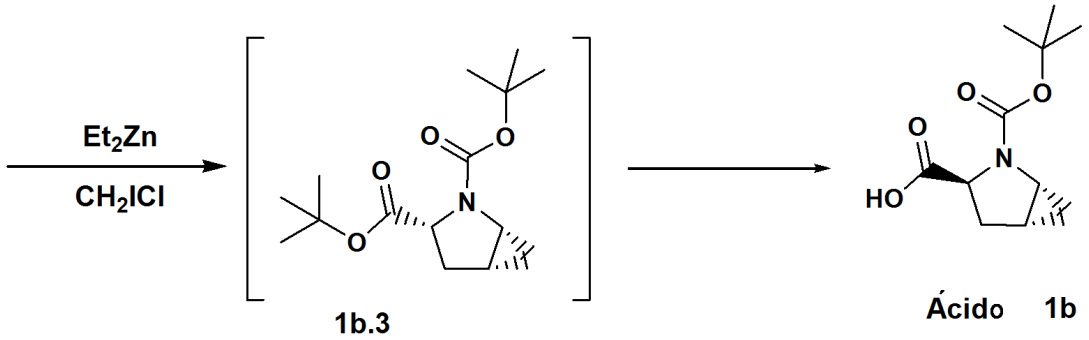
la amida 1a y 250 ml de isopropanol. La suspensión resultante se cargó después con 252 ml de NaOEt al 23% en peso en EtOH (2.68 M, 675 mmol, 3.0 eq.) y se agitó a 50°C durante alrededor de 1 hora. 1h. La mezcla se cargo con 12.2 ml (675 mmol, 3 eq.) de agua y se calentó a 60°C. La suspensión resultante se dejó agitar a 60°C durante alrededor de 18 horas. 18h. La suspensión se enfrió a temperatura ambiente y se cargó con 250 ml de agua y con 98.2 g (450 mmol, 2.0 eq.) de di-*t*-butildicarbonato. Se eliminaron el etanol y el isopropanol por medio de destilación *en el vacío* y la mezcla acuosa se enfrió a 0°C. La mezcla se neutralizó con 76 ml (456 mmol) de HCl acuoso 6M manteniendo mientras una temperatura interna < 5°C. El producto se extrajo con 500 ml de MTBE y la capa orgánica rica se lavó con 100 ml de agua. La solución transparente se concentró hasta 150 ml por medio de destilación en el vacío y la suspensión resultante se cargó con 600 ml de heptano manteniendo mientras una temperatura interna > 45°C. La suspensión se enfrió a ta durante alrededor de 30 min y se dejó agitar a ta durante alrededor de 2 horas. El producto se filtró, se lavó con 250 ml de heptano:MTBE en una proporción de 4:1 y se secó a vacío a 70 °C dando 40.5 g (178 mmol, rendimiento del 79%, 99.8 AP a 205 nm) de ácido 1b: RMN de ^{1}H (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 4.02-3.80 (m, 1H), 3.45-3.15 (m, 1H), 2.40-2.19 (m, 1H), 2.19-2.0 (m, 1H), 1.70-1.50 (m, 1H), 1.50-1,20

(m, 9H), 0.83-0.60 (m, 1H), 0.33-0.55 (m, 1H); RMN de ^{13}C (100 MHz, DMSO-d_6) δ 173.7, 173.2, 155.0, 154.3, 79.4, 60.5, 60.2, 37.6, 32.6, 31.8, 28.4, 28.2, 15.6, 15.2, 14.4; HRMS calculado para $C_{11}H_{18}NO_4$ (M + H; IEP$^+$): 228.1236. Encontrado: 228.1234.

Síntesis alternativa de ácido 1b



1b.1 1b.2



1b.3 Ácido 1b

En un reactor de 500 ml se disolvió ester de reactor 1b.1 (comercialmente disponible, 17.5 g, 1.00 equiv.) en THF (87.5 ml). La solución resultante se enfrió a -75°C y DIBAL-H 1.5 M en tolueno (61.3 ml, 1.5 equiv.) se cargó manteniendo mientras la temperatura por debajo de -70°C. La solución resultante se agitó a -70°C durante 1 hora. Se cargó ácido teifluoroacético (2.3 ml, 0.5 equivalentes) durante 10 minutos manteniendo la temperature interna por debajo de -

70°C. Se cargó ácido trifluoroacético manteniendo mientras la temperatura por debajo de -70°C. La solución resultante se agitó a -70°C durante 1 hora. Se cargo ácido trifluoroacético (2.3 ml, 0.5 equiv.) durante 10 minutos manteniendo la temperatura interna por debajo de -70°C. Se cargó después trietilamina (51.3 ml, 6 equiv.) durante 15 minutos manteniendo la temperatura interna por debajo de -70°C. Se cargó anhídrido trifluoroacético (11.2 ml, 1.3 equiv.) durante 10 minutos manteniendo la temperatura interna por debajo de -70°C. La reacción se dejó después calendar a temperatura ambiente durante 90 minutos y se desactivó por medio de adición inverse a una solución de monohidrato de ácido cítrico acuoso al 20% (96.6 g, 1.5 equiv.) manteniendo mientras una temperatura por debajo de 15°C. La mezcla resultante se agitó a temperature ambiente durante 2 horas después se descartó la fase acuosa inferior. La fase orgánica rica en producto se lavó dos veces con 70 ml de bicarbonate de sodio acuoso saturado. El bicarbonato de sodio sólido (1.7 g, 0.1 g/g Ejemplo 146) se cargó y la solución se cambió de disolvente en tolueno puro a vacío proporcionando 1b.2 como una solución en 2L/kg de tolueno.

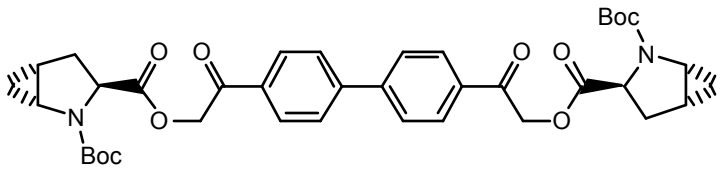
Se filtró a través de filtro pulidor una solución de 1b.2 (16.5 g teóricos del Ejemplo 151) en 33 ml de tolueno en un reactor de 250 ml. Se cargó después trifluorotolueno (50 ml) y cloroyodometano (43.2 g, 4.0 equiv.) y la solución

resultante se enfrió a -20°C. Se cargó dietilcinc 1.1 M en tolueno (111 ml, 2.0 equiv.) manteniendo mientras la temperatura ambiente por debajo de -8°C. La solución resultante se agitó a -15 a -20°C durante 14 horas. La mezcla de reacción se calentó a 0°C después se desactivó por medio de adición inversa a una solución de ácido cítrico acuosa de 20% en peso (135.7 g, 2.3 equiv.). El reactor se aclaró con tolueno (82 ml) y el aclarado se añadió a la solución de desactivación. La mezcla bifásica resultante se agitó durante 20 minutos después de que la fase acuosa inferior se separa y descarta. La fase orgánica rica se lavó dos veces con 60 ml de NaCl acuoso al 13% en peso seguida por 60 ml de $NaHCO_3$ saturado. La solución resultante se sometió a cambio de disolvente en IPA puro al vacío proporcionando Ib.3 como una solución en 10 l/kg de IPA.

Se cargó un reactor de 250 ml con una solución de 1b.3 (147 ml, 14.7 g teóricos de ester 1b.1) en IPA. La solución se calentó a 35°C y se añadió hidróxido de sodio acuoso (6.2 g, 3.0 equiv.). La mezcla resultante se agitó a 35°C durante toda una noche. Se añadió agua (44 ml) y los solventes orgánicos se retiraron al vacío. Se añadió MTBE (145 ml) y el pH se ajustó a 3.0 con HCl acuoso 6 N. La fase acuosa se separó y descartó. El producto orgánico rico se lavó con 60 ml de agua y después se secó azeotrópicamente al vacío por medno de adición constante de volumen de MTBE. La

solución se concentró a 55 ml y se agitó a 50°C durante 30 minutos. La solución se enfrió a temperatura ambiente durante 1 hora tiempo durante el que se formó una suspensión. Se cargó heptano (90 ml) durante 90 minutos y la suspensión resultante de dejó madurar durante 1 hora. Los sólidos se recogieron en un vidrio poroso de tamaño medio y se lavaron con 22.5 ml de heptano:MTBE 3:1 seguido por 22.5 ml de heptano. El sólido canela se secó en un horno al vacío de a 50°C proporcionando 5.48 g (46%) de ácido 1b con pureza de LCAP de 94.9. El ácido en bruto 1b se disolvió en 55 ml de MTBE, MTBE a 50°C. La solución resultante se concentró a 20 ml y se enfrió a temperatura ambiente durante 1 hora. Se añadió después heptano (33 ml) durante 90 minutos. Los sólidos resultantes se recogieron en un vidrio poroso de tamaño medio, se lavó con heptano (15 ml), y se secó en un horno al vacío a 50°C proporcionando 4.45 g de ácido 1b en forma de un polvo canela (98.8 AP, pureza quiral del 98.8%, 37% a partir del éster 1b.1).

Ejemplo 1, Etapa c

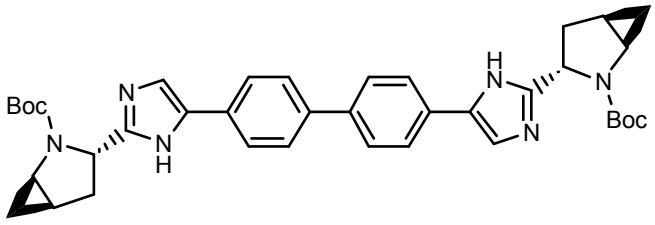


Un matraz de fondo redondo de 250 ml equipado con una entrada para nitrógeno, un agitador aéreo y un termoacoplador se cargó con 20.0 g (88.0 mmol, 2.11 eq.) de

ácido 1b, 16.5 g (41.7 mmol, 1 eq.) de 1.1'-(bifenil-4,4'-diil)bis(2-bromoetanona), 110 ml de acetonitrilo y 55 ml de tetrahidrofurano. Después, se cargó diisopropiletilamina (15.1 ml, 86.6 mmol, 2.08 eq.) manteniendo una temperatura interna < 25 °C. La mezcla se dejó agitar a 20-25 °C durante aproximadamente 5 horas y se cargó con 83 ml de acetato de etilo y 90 ml de NaCl acuoso al 13% en peso. Se separó la mezcla bifásica resultante y la fase orgánica rica se lavó con 90 ml adicionales de NaCl acuoso al 13% p. La capa orgánica rica se diluyó con 20 ml de tetrahidrofurano y se lavó con una mezcla acuosa de $NaHCO_3$ y NaCl (45 ml de $NaHCO_3$ acuoso 1M y 45 ml de 26% de NaCl acuoso). La capa orgánica rica se intercambió con disolvente en tolueno mediante destilación *al vacío* hasta obtener un volumen diana de aproximadamente 160 ml. La solución en tolueno resultante del cetoéster 1c se usó como tal en la etapa siguiente.

[Nota: para la preparación de 1.1'-(bifenil-4,4'-diil)bis(2-bromoetanona), véase el proceso en la solicitud de patente WO2009/020825].

Ejemplo 1, Etapa d

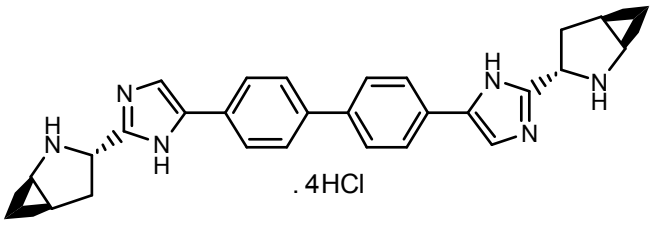


La anterior solución en tolueno de cetoéster 1c se

cargó con 64.2 g (832.9 mmol, 20.0 eq.) de NH_4OAc y se dejó agitar a 90-100 °C durante aproximadamente 18 horas. Se enfrió hasta 60 °C y se cargó con 255 ml de AcOH:agua en una proporción de 2:1. Se separó la mezcla bifásica resultante y la capa de tolueno se lavó con 58 ml de AcOH:agua en una proporción de 1:1. Las capas acuosas ricas se combinaron y el tolueno residual se eliminó mediante destilación al vacío. La solución acuosa se diluyó con 60 ml de metanol y se calentó hasta 50-60 °C. Se cargó con 106 ml (1060 mmol, 25.4 eq.) de NaOH 10 N manteniendo una temperatura interna < 60 °C. A continuación, la suspensión espesa resultante se enfrió hasta la temperatura ambiente. La suspensión espesa se filtró y se lavó con 100 ml de agua, seguidos por 400 ml de metanol, dando 26.1 g de imidazol bruto 1d. El imidazol 1d bruto húmero se cargó después en un matraz de fondo redondo de 500 ml equipado con una entrada para nitrógeno, un agitador aéreo y un termoacoplador. Se cargó con 165 ml de N-metil-2-pirrolidinona y se calentó hasta 50°C. La solución transparente resultante se cargó con 30 ml de metanol y se dejó agitar a 50°C durante aproximadamente 18 horas. La suspensión espesa resultante se cargó 130 ml adicionales de metanol manteniendo una temperatura interna > 45 °C. La suspensión espesa se dejó agitar a 50°C durante aproximadamente 30 minutos y se enfrió hasta la temperatura ambiente. La suspensión espesa se filtró y los sólidos se

lavaron con 90 ml de metanol:N-metil-2-pirrolidinona en una proporción de 1:1, seguido por 200 ml de metanol. Los sólidos se secaron al vacío a 70 °C, dando 22.7 g (31.5 mmol, rendimiento del 76%, 95 AP a 254 nm) d imidazol 1d: RMN de ^{1}H (400 MHz, DMSO-d_6) δ ppm 11.95 (s, 2H), 7.89-7.76 (d, 4H), 7.74-7.60 (d, 4H), 7.50 (s, 2H) 4.62 (s, 2H), 3.55-3,30 (m, 2H), 2.45-2,20 (m, 4H), 1.70-1.59 (m, 2H), 1.59-0.90 (s, 18H), 0.83-0.69 (m, 2H), 0.65-0.49 (m, 2H); HRMS calculado para $C_{38}H_{45}N_6O_4$ (M + H; ESI$^+$): 649.3502; Encontrado: 649.3524.

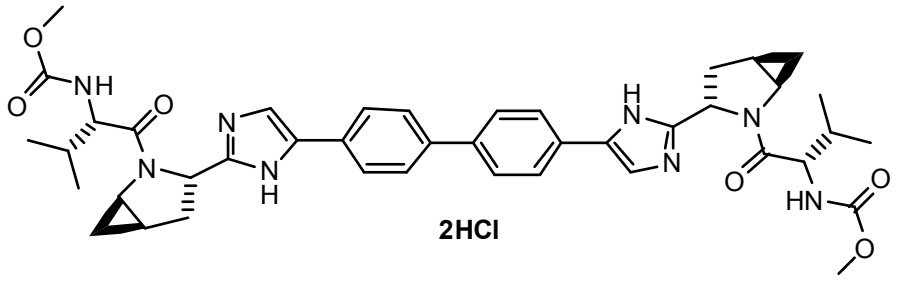
Ejemplo 1, Etapa e



Un matraz de fondo redondo de 250 ml equipado con una entrada para nitrógeno y un agitador aéreo se cargó con 7.0 g (10.8 mmol) del imidazol 1d, 105 ml de metanol y 3.7 ml (20.8 mmol, 1.93 eq.) de HCl 5.6M en isopropanol. La solución resultante se trató con carbón y se filtró. El carbón se lavó con 140 ml de metanol y se combinó con el filtrado. La corriente orgánica rica se concentró hasta aproximadamente 70 ml y se cargó en un matraz de fondo redondo equipado con una entrada para nitrógeno, un agitador aéreo y un termoacoplador. La solución se cargó después con 14.75 ml (88.5 mmol, 8.2 eq.) de HCl 6M y se dejó agitar a

50°C. Después de aproximadamente 12 horas a 50 °C, la mezcla se carbón con 50 ml de isopropanol y la suspensión espesa resultante se dejó agitar a 50°C durante 1 hora. La suspensión espesa se enfrió hasta la temperatura ambiente y se envejeció durante aproximadamente 15 horas. El producto se filtró y se lavó con 35 ml de isopropanol:metanol a 4:1, seguido por 70 ml de isopropanol. Los sólidos se secaron a 55°C al vacío, dando 5.3 g (8.9 mmol, rendimiento del 83%, 99.8 AP a 254 nm) de pirrolidina 1e/4HCl: RMN de ^{1}H (400 MHz, DMSO-d_6) δ 14.00 9.38 (s ancho, 8H), 8.31 (s, 2H), 8.06-7.96 (d, 4H), 7.94-7.84 (d, 4H), 5.05-4.89 (dd, 2H), 3.55-3.42 (m, 2H), 2.87-2.69 (dt, 2H), 2.64-2.53 (dd, 2H), 2.05-1.89 (m, 2H), 1.17-0.98 (m, 2H), 0.96-0.82 (dd, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.0, 139.3, 133.6, 127.2, 126.6, 125.8, 116.6, 49.8, 34.3, 29.9, 15.2, 5.3; HRMS calculado para $C_{28}H_{29}N_6$ (M + H; ESI$^+$) 449.2454; Encontrado: 449.2470.

Ejemplo 1, Etapa f



2HCl

Un reactor con camisa de 250 ml equipado con una entrada para nitrógeno, un agitador aéreo y un termoacoplador se cargó con 4.24 g (24.2 mmol, 2.4 eq.) de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (25.21 mmol, 2.5 eq.),

1-hidroxibenzotriazol monohidrato, 4.55 g (23.73 mmol, 2.35 eq.) de clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida y 60 ml de acetonitrilo. La mezcla se agitó durante aproximadamente 1 hora y se cargó con 6 g (10.1 mmol) de pirrolidina 1e/4HCl. La suspensión espesa resultante se enfrió hasta 10°C y se cargó con 7.92 ml (45.41 mmol, 4.5 eq.) de diisopropiletilamina. La mezcla se dejó calentar hasta la temperatura ambiente y se agitó durante aproximadamente 19 horas. La solución orgánica resultante se lavó con 36 ml de NaCl acuoso al 13% en peso. La capa orgánica rica se cargó con 12 ml de acetonitrilo y se lavó con 36 ml de una solución acuosa que contenía NaCl acuoso al 13% en peso de NaOH 1M. Después, la capa orgánica rica se cargó con 12 ml de metanol y se calentó hasta 50°C. se añadió agua (60 ml) durante un periodo de 2 horas y la suspensión espesa resultante se enfrió hasta la temperatura ambiente y se envejeció durante aproximadamente 2 horas. Los sólidos se filtraron, se lavaron con 36 ml de acetonitrilo:agua a 1:1 y se secaron al vacío. Un reactor con camisa de 250 ml equipado con una entrada para nitrógeno, un agitador aéreo y un termoacoplador se cargó con los sólidos anteriores y se disolvió con 240 ml de etanol de grado SDA3A. La solución se concentró hasta aproximadamente. 50 ml mediante destilación al vacío y se cargó con 4.24 ml (23.19 mmol, 2.30 eq.) HCl 5.47 M en isopropanol y 30 ml adicionales de etanol

SDA3A. La mezcla se concentró hasta aproximadamente 50 ml, se diluyó con 40 ml de etanol SDA3A y se trató con carbón. El carbón se filtró y se lavó con 90 ml de etanol SDA3A. El filtrado y lavado ricos se combinaron y se concentraron hasta 40 ml. Se cargaron 16 ml de acetato de etilo y se calentó hasta 40 °C. Se cargaron 60 mg de cristales de semilla de amida 1f/2HCl y se agitó a 40°C durante 1 hora. Se cargaron 68 ml adicionales de acetato de etilo durante 1.5 horas manteniendo una temperatura interna de 40 °C. La suspensión espesa resultante se agitó a 40°C durante aproximadamente 18 horas y se enfrió hasta la temperatura ambiente. La suspensión espesa se filtró y se lavó con 24 ml de acetato de etilo:etanol SDA3A en una proporción de 3:1 y 30 ml de acetato de etilo. Los sólidos se secaron a 50°C al vacío, dando 6.83 g (8.17 mmol, rendimiento del 81%, 99.5 AP a 300 nm) de amida 1f/2HCl: RMN de ^{1}H (600 MHz, DMSO-d_6) δ 15.51 (s, 2H), 14.95 (s, 2H) 8.19 (s, 2H), 8.05 (d, 4H), 7.91 (d, 4H), 7.25 (d, 2H), 5.18 (t, 2H), 4.44 (t, 2H), 3.77 (s, 2H), 3.55 (s, 6H), 2.50 (m, 2H), 2.39 (m, 2H), 2.24 (m, 2H), 1.91 (m, 2H), 0.95 (m, 2H), 0.92 (d, 6H), 0.81 (d, 6H), 0.75 (s, 2H); RMN de ^{13}C (125 MHz, DMSO-d_6) δ 172.7, 156.9, 148.5, 139.1, 131.7, 127.1, 126.5, 125.9, 115.1, 57.8, 54.5, 51.5, 37.3, 32.9, 29.2, 19.7, 17.5, 17.5, 15.7; Análisis Elemental Calculado (corregido para 0.81% de agua): C = 59.86%, H = 6.30%, N = 13.29%, Cl = 8.41%; Encontrado: C =

59.99%, H = 6.27%, N = 13.12%, Cl = 8.42%.

Preparación de la siembra para la amida 1f/2HCl: La amida 1f se preparó de acuerdo con el procedimiento básico indicado en lo que antecede usando 504 mg (0.8 mmol) de pirrolidina 1e.4HCl. Una vez finalizada la reacción, la solución rica en acetonitrilo se lavó con 3 ml de NaCl acuoso al 13%, 2 x 3 ml de una solución acuosa que contiene 13% de NaCl y NaOH 1M y 3 ml de NaCl acuoso al 13%. La capa orgánica rica se concentró hasta obtener un residuo y se diluyó con 10 ml de acetonitrilo. La mezcla turbia se filtró y el filtrado transparente se concentró hasta un residuo. El residuo se diluyó con 10 ml de etanol SDA3A y se cargó con 2.1 ml (1.9 mmol, 2.4 eq.) de HCl 0.88M en etanol. La mezcla se concentró hasta obtener un residuo y se diluyó con 1.8 ml de isopropanol. La solución resultante se calentó hasta 50 °C y se dejó agitar durante aproximadamente 18 horas. La suspensión espesa resultante se enfrió hasta la temperatura ambiente y se lavó con acetona:etanol en una proporción de 2:1, dando 476 mg (0.57 mmol, 78%) de la amida 1f/2HCl.

[Nota: El ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico se adquirió en Flamma]

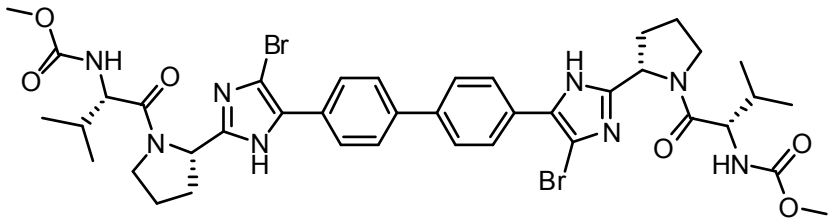
Ejemplos 1 y 2

Una muestra de la amida 11f/2HCl (106.9 mg) no tenía base (columna 2 g MCX; lavado con MeOH; elución con NH_3/MeOH 2 N) y se secó *al vacío*. Se añadió NCS (0.0195 g,

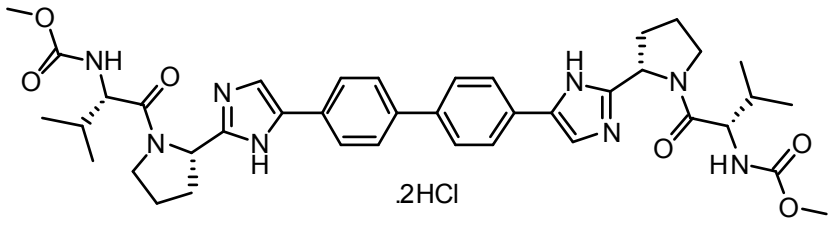
0.146 mmol) hasta una solución en DMF (2.5 ml) del material resultante y se calentó con un baño de aceite a 50 °C durante 16.5 horas. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) recuperando las sales en TFA del Ejemplo 1 (espuma blanca; 56.1 mg) y del Ejemplo 2 (espuma blanca; 22.3 mg). Ejemplo -1: RMN de ^{1}H (DMSO-d_6, δ = 2.50 ppm, 400 MHz): 12.61 (br s, 1H), 8.13 (s, 1H), 7.93 (d, *J* = 8.5, 2H), 7.90-7.86 (m, 4H), 7.82 (d, *J* = 8.5, 2H), 7.27 (d, *J* = 8.3, 1H), 7.17 (d, *J* = 8.5, 1H), 5.02-4.94 (m, 2H), 4.44-4.38 (m, 1.80H), 4.31 (app s ancho, 0.2H), 3.75 (m, 1H), 3.62 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 2.56-2.50 ('m' parcialmente solapado con señal disolvente, 1H), 2.41-2,23 (m, 3H), 2.17-2.09 (m, 1H), 2.07-2.00 (m, 1H), 1.97-1.91 (m, 1H), 1.88-1.81 (m, 1H), 1.01-0.81 (m, 15H), 0.71 (m, 1H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL/EM (Cond. 1A): T_r = 1.80 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{50}ClN_8O_6$: 797.35; encontrado 797.33. Ejemplo -2: RMN de ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): 7.86 (d, *J* = 8.6, 4H), 7.80 (d, *J* = 8.5, 4H), 7.17 (d, *J* = 8.5, 2H), 4.96 (dd, *J* = 7.5, 6.0, 2H), 4.40 (app t, *J* = 7.8, 2H), 3.61 (m, 2H), 3.54 (s, 6H), 2.33-2,23 (m, 4H), 2.09-1.98 (m, 2H), 1.90-1.82 (m, 2H), 1.01-0.82 ('m' solapado y dos 'd' a 0.96 ppm y 0.87 ppm con *J* = 6.8 y *J* = 6.5, respectivamente; 14H); 0.71 (m, 1.7H),

0.62 (m, 0.3H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL/EM (Cond. 1A): T_r = 2.79 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{49}Cl_2N_8O_6$: 831.32; encontrado 831.26.

Ejemplo 3



Ejemplo 3, Etapa a

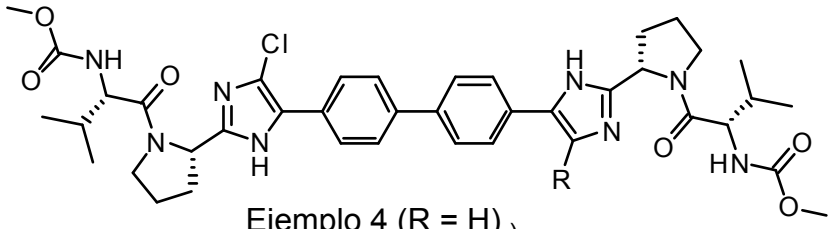


Para la síntesis de la amida 3a/2HCl, véase el procedimiento de la solicitud de patente WO2009/020825.

Ejemplo 3

A una solución de la amida 3a (32 mg, 0.043 mmol) en ácido acético (2 ml) se añadieron 2 eq. de bromo 1M en ácido acético y la reacción se agitó durante 30 minutos. Se añadió 1 eq. adicional de bromo (se formaron sólidos) y la reacción se neutralizó con 5% de $NaHCO_3$ y se extrajo con EtOAc (2 x 10 ml). Los extractos combinados se lavaron con una solución de $Na_2S_2O_3$ saturado y salmuera y se concentraron. El residuo se secó en alto vacío, dando el Ejemplo 3 (41 mg). CL/EM (Cond. J4): Tr = 3.54 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{49}Br_2N_8O_6$: 897.22; encontrado 897.28.

Ejemplos 4 y 5

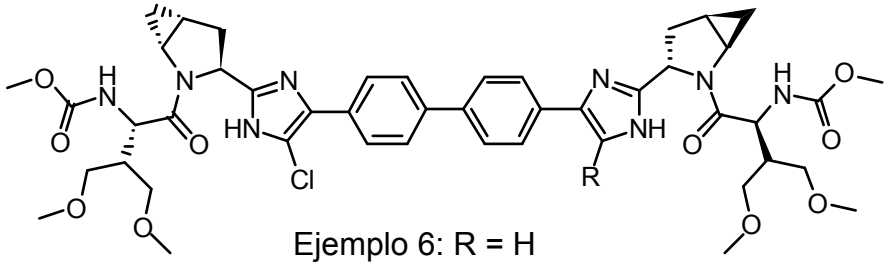


Ejemplo 4 (R = H)
Ejemplo 5 (R = Cl)

A una mezcla de la amida 3a (197 mg, 0.243 mmol) y N-clorosuccinimida (39 mg, 0.292 mmol) en acetonitrilo (2 ml) se añadió diisopropiletilamina (100 ul, 74.2 mg, 0.574 mmol) y se agitó durante la noche. Después, a la mezcla de reacción se añadió una porción adicional de N-clorosuccinimida (66 mg, 0.494 mmol) y se agitó hasta que se confirmó mediante análisis HPLC el consumo del material de partida. Después, la mezcla de reacción bruta se purificó mediante HPLC de fase inversa (Disolvente A = H_2O/CH_3CN (95:5) + 0.05% de TFA; Disolvente B = H_2O/CH_3CN (5:95) + 0.05% de TFA; Columna: Luna C18, 5u, 100 × 21.5 mm; Caudal: 20 ml/min), dando las sales en TFA del Ejemplo 4 (polvo amorfo amarillento, 60 mg) y del Ejemplo 3 (polvo amorfo amarillento, 115 mg). Ejemplo 5: CL/EM (Cond. *3*): T_r = 6.13 min. RMN de ^1H (DMSO-d_6, TMS, 600 MHz): 8.16 (s, 1H), 7.95-7.91 (m, 7H), 7.85 (d, *J* = 8.8, 2H), 7.35 (d, *J* = 8.4, 1H), 7.32 (d, *J* = 8.4, 1H), 5.19 (t, *J* = 7.3, 1H), 5.05 (m, 1H), 4.15 (t, *J* = 7.7, 1H), 4.08 (t, J = 8.1, 1H), 3.88-3.81 (m, 4H), 3.56 (s, 6H), 2.43 (m, 1H), 2.21-2.11 (m, 4H), 2.08-2.05 (m, 2H), 1.97 (m, 3H),

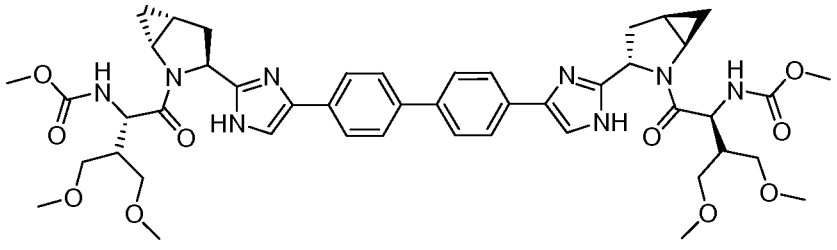
0.91 (d, J = 6.5, 3H), 0.87 (d, J = 7.0, 3H), 0.85 (d, J = 7.0, 3H), 0.80 (d, J = 6.6, 3H). EMAR: Calculado para [M+H]+ $C_{40}H_{50}ClN_8O_6$: 773.3542; encontrado 773.3530. Ejemplo 4: CL/EM (Cond. 3): Tr = 8.61 min. RMN de 1H (DMSO-d6, TMS, 600 MHz): 7.89 (d, J = 8.3, 4H), 7.83 (d, J = 8.3, 4H), 7.33 (d, J = 8.4, 2H), 5.05 (m, 2H), 4.09 (t, J = 8.3, 2H), 3.84-3.81 (m, 4H), 3.56 (s, 6H), 2.24-2.15 (m, 4H), 2.00-1.95 (m, 6H), 0.91 (d, *J* = 6.7, 6H), 0.87 (d, *J* = 6.6, 6H). EMAR: calculado para $[M+H]^+$ $C_{40}H_{49}Cl_2N_8O_6$: 807.3152; encontrado 807.3138.

Ejemplos 6 y 7



Ejemplo 6: R = H
Ejemplo 7: R = Cl

Ejemplo 6, Etapa a



A una mezcla de pirrolidina 1e/4HCl (0.104 g, 0.174 mmol), HATU (0.133 g, 0.349 mmol) y Cap-193 (0.082 g, 0.349 mmol) en DMF se añadió DIEA (0.183 ml). La mezcla de

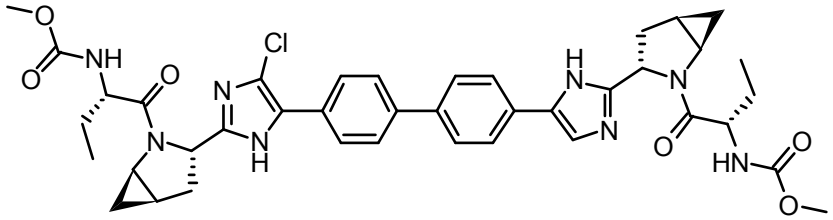
reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se purificó por HPLC preparatoria (columna Phenomenex AXIA 5 u, gradiente de 35 min a partir de B al 0-90%. A = $H_2O/CH_3CN/NH_4OAc$ 10 mM, 95:5. B = CH_3CN/H_2O/NH4OAc 10 mM 95:5) proporcionando Ejemplo 6, Etapa a (0.064 g). CL/EM: anal. calcd. para [M+H]+ $C_{46}H_{59}N_8O_{10}$: 883.43; encontrado: 883.26. RMN de ^1H (400 MHz, MeOD) ppm 7.90 (2 H, s), 7.78 – 7.86 (8 H, m), 5.13 (2 H, dd, J=9.2, 6.9 Hz), 4.96 (2 H, d, J=5.0 Hz), 3.73 – 3.79 (2 H, m), 3.63 (6 H, s), 3.39 – 3.49 (6 H, m), 3.35 (1 H, d, J=4.8 Hz), 3.32 - 3.34 (1 H, m), 3.30 (6 H, s), 3.15 (6 H, s), 2.66 (2 H, dd, J=13.5, 9.4 Hz), 2.37 - 2.51 (4 H, m), 2.02 - 2.09 (2 H, m), 1.03 - 1.14 (2 H, m), 0.81 - 0.93 (2 H, m).

Ejemplos 6 y 7

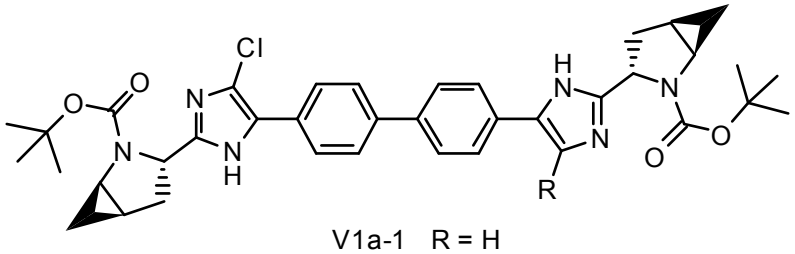
A una solución de Ejemplo 6, Etapa a (0.057 g) en DMF se añadió NCS (10.34 mg, 0.077 mmol). La mezcla de reacción se calentó a 60°C durante 3 horas. La mezcla de reacción se purificó por HPLC preparatoria (Phenomenex AXIA 5 u columna de 30 x 100 mm, gradiente de 20 min desde 0-100% de B. A = H_2O/CH_3OH/TFA 90:10:0.1. B = CH_3OH/H_2O/TFA 90:10:0.1) proporcionando Ejemplo 6 (0.022 g) y Ejemplo 7 (0.017 g). Ejemplo 6: CL (Cond. J5): Tr = 3.46 min. CL/EM: anal. calcd. para [M+H]+ $C_{46}H_{58}ClN_8O_{10}$: 917.39; encontrado: 917.12. RMN de ^1H (400 MHz, MeOD) ppm 7.87 - 7.91 (1 H, m), 7.77 - 7.86 (8 H, m), 5.14 (1 H, dd, J=9.2, 6.9 Hz), 5.05 (1 H, dd, J=8.1, 6.3

Hz), 4.96 (2 H, t, J=5.7 Hz), 3.73 - 3.79 (1 H, m), 3.67 - 3.72 (1 H, m), 3.57 - 3.66 (6 H, m), 3.32 - 3.51 (8 H, m), 3.29 (6 H, d, J=1.8 Hz), 3.19 (3 H, s), 3.12 - 3.16 (3 H, m), 2.60 - 2.72 (1 H, m), 2.32 - 2.54 (5 H, m), 2.02 (2 H, d, J=6.3 Hz), 1.00 - 1.19 (2 H, m), 0.88 (1 H, s ancho), 0.82 (1 H, s ancho). Ejemplo 7: CL (Cond. PY1): Tr = 4083 min. CL/EM: anal. calcd. para [M+H]+ $C_{46}H_{56}Cl_2N_8O_{10}$: 951.35; encontrado: 951.09. RMN de ^{1}H (400 MHz, MeOD) ppm 7.74 - 7.84 (8 H, m), 5.05 (2 H, t, J=7.2 Hz), 4.95 (2 H, d, J=5.5 Hz), 3.66 - 3.72 (2 H, m), 3.63 (6 H, s), 3.37 - 3.53 (8 H, m), 3.30 (6 H, s), 3.19 (6 H, s), 2.32 - 2.51 (6 H, m), 1.92 - 2.06 (2 H, m), 1.08 (2 H, dt, J=8.6, 5.8 Hz), 0.81 (2 H, d, J=1.8 Hz).

Ejemplo V1.



Ejemplo V1, Etapa a



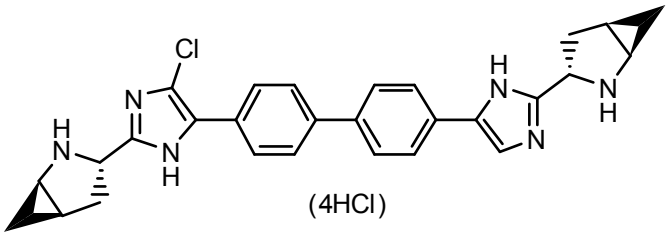
V1a-1 R = H
V1a-2 R = Cl

Una solución de carbamato 1d (0.80 g, 1.23 mmol) y NCS (0.214 g, 1.603 mmol) en DMF (12 ml) se calentó a 50 °C durante 17 horas. Después de dejar que se enfriara hasta la

temperatura ambiente se eliminaron los componentes volátiles *al vacío*. El residuo se disolvió en MeOH (36 ml) y los dos productos se separaron mediante HPLC preparativa (Columna: XTERRA, 30 X 100 mm, S5; % inicial de B = 50, % final de B = 100; Tiempo de gradiente = 10 min; Tiempo de detención = 12 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de MeOH – 90% de H_2O – 0.1% de TFA; Disolvente B = 90% de MeOH – 10% de H_2O – 0.1% de TFA). Cada una de las dos fracciones se neutralizaron con una solución en exceso de NH_3/MeOH 2N y se concentraron *al vacío* eliminando la mayoría del metanol y el residuo se repartió entre 20% de MeOH/$CHCl_3$ y agua. La capa orgánica se secó ($MgSO_4$), se filtró y se concentró *al vacío*, dando cloruro V1a-1 (espuma de color amarillo claro; 288.4 mg) y dicloruro V1a-2 (sólido de color amarillo claro; 400.4 mg). Cloruro V1a-1: RMN de ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.62-12.60 (m, 1H), 12.23 (s, 0.2H), 11.92 (s, 0.8H), 7.85-7.32 (m, 9H), 4.68-4,42 (m, 2H), 3.47-3,38 (m, 2H), 2.40-2.35 (m, 2H), 2.26-2,20 (m, 2H), 1.71-1.58 (m, 2H), 1.55-0.96 (app s ancho, 18H), 0.82-0.69 (m, 2H), 0.64-0.51 (m, 2H). CL (V-Cond. 1): T_r = 2.44 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{38}H_{44}ClN_6O_4$: 683.31; encontrado: 683.31. Dicloruro V1a-2: RMN de ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.62 (s, 2H), 7.85 (d, *J* = 8.8, 4H), 7.82 (d, *J* = 8.9, 4H), 4.61-4,42 (m, 2H), 3.53-3,38 (m, 2H), 2.41-2.35 (m, 2H), 2.27-2,20 (m, 2H), 1.70-1.59 (m, 2H),

1.53-0.94 (app s ancho, 18H), 0.80-0.70 (m, 2H), 0.64-0.53 (m, 2H). CL (Cond. 1A): T_r = 2.89 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{38}H_{43}Cl_2N_6O_4$: 717.27; encontrado: 717.31.

Ejemplo V1, Etapa b



A una suspensión de cloruro V1-a (0.2741 g, 0.401 mmol) en MeOH (1 ml) se añadió HCl 4M en dioxano (4 ml). La mezcla se agitó a temperatura ambiente durante 7 horas y, después, se eliminó el componente volátil *al vacío* dando la sal HCl de V1b en forma de un sólido marrón (231.7 mg). El producto se usó sin purificación adicional. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 13.51 (s ancho, 1H), 10.53-10.30 (m, 2H), 9.87-9.72 (m, 1H), 8.02-7.85 (m, 9H), 4.72-4.68 (m, 1H), 4.65-4.53 (m, 1H), 3.42-3,30 (m, 2H), 2.68-2.37 ('m' parcialmente solapado con señal de disolvente, 4H), 1.97-1.87 (m, 2H), 1.16-1.07 (m, 2H), 0.89- 0.80 (m, 2H). CL (Cond. 1A): T_r = 1.66 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{28}H_{28}ClN_6$: 483.21; encontrado: 483.20. [Nota: el contenido exacto en HCl del producto no se determinó].

Ejemplo V1.

A una solución de cloruro V1b/4HCl (0.045 g, 0.072 mmol), ácido (S)-2-(metoxicarbonilamino)butanoico (0.025 g,

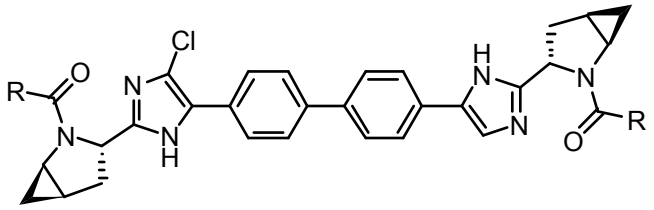
0.157 mmol) y N,N-diisopropiletilamina (0.075 ml, 0.429 mmol) en DMF (1.5 ml)se añadió HATU (0.057 g, 0.150 mmol). La mezcla de reacción se agitó a ~25 °C durante 1 hora.

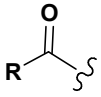
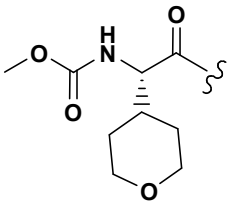
Se diluyó con MeOH (2.5 ml) y el producto se purificó mediante HPLC (Columna: XTERRA, 30 X 100 mm, S5; % inicial de B = 30, % final de B = 90; Tiempo de gradiente = 10 min; Tiempo de detención = 12 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de MeOH – 90% de H_2O – 0.1% de TFA; Disolvente de B = 90% de MeOH – 10% de H_2O – 0.1% de TFA), dando las sales en TFA del Ejemplo V1 en formar de un sólido amarillo claro (39.4 mg). RMN de ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.80-14.36 (m ancho, 1.4H), 12.58 (app s ancho, 0.6H), 8.14 (s, 1H), 7.94 (d, *J* = 8.5, 2H), 7.89 (d, *J* = 8.3, 2H), 7.87 (d, *J* = 8.4, 2H), 7.82 (d, *J* = 8.6, 2H), 7.38 (d, *J* = 7.8, 0.9H), 7.28 (d, *J* = 7.8, 0.9H), 7.07 (app s ancho, 0.1H), 6.96 (app s ancho, 0.1H), 5.02 (dd, *J* = 8.8, 6.8, 1H), 4.96 (dd, *J* = 7.0, 6.0, 1H), 4.50-4.39 (m, 2H), 3.74-3.67 (m, 1H), 3.59-3.48 (m, 7H), 2.60-2.47 ('m' parcialmente solapado con señal de disolvente, 1H), 2.42-2,22 (m, 3H), 2.01-1.65 (m, 4H), 1.65-1.52 (m, 2H), 1.06-0.84 (m, 8H), 0.83-0.77, (m, 1H), 0.74-0.66 (m, 1H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. CL (Cond. 1A): T_r = 1.66 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{40}H_{46}ClN_8O_6$: 769.32; encontrado: 769.35.

Ejemplo V2.

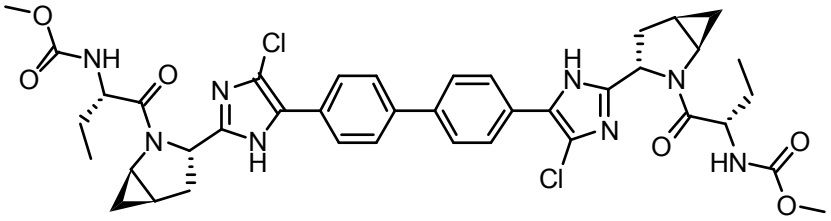
El Ejemplo V2 (sal en TFA) se preparó a partir de

la pirrolidina V1b /HCl y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético de acuerdo con el procedimiento descrito para la preparación del Ejemplo V1.

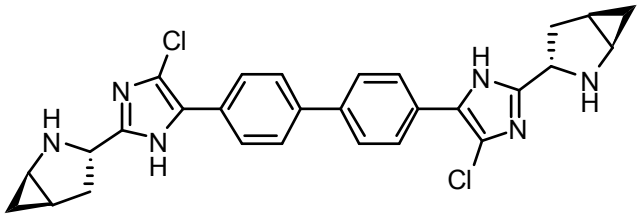


Ejemplo		T_a (CL-Cond.); CL (Cond. 2a y 2b): Índice de homogeneidad en %; Datos de EM
V2		2.06 min (Cond. 1A); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{46}H_{54}ClN_8O_8$: 881.38; encontrado: 881.36.

Ejemplo V3



Ejemplo V3, Etapa a



El intermedio V3a se preparó en forma de una

sal HCl de carbamato V1a-2 de acuerdo con el procedimiento descrito para la preparación de pirrolidina V1b. RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.62-10.48 (m, 2H), 9.92-9.75 (m, 2H), 7.92 (d, *J* = 8.8, 4H), 7.89 (d, *J* = 9.1, 4H), 4.68-4.57 (m, 2H), 3.40-3,31 (m, 2H), 2.54-2.50 ('m' parcialmente solapado con señal de disolvente, 2H), 2.46-2.39 (m, 2H), 1.91-1.85 (m, 2H), 1.16-1.07 (m, 2H), 0.85-080 (m, 2H). CL (Cond. 1A): T_r = 2.01 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{28}H_{27}Cl_2N_6$: 517.17; encontrado: 517.06. [Nota: el contenido exacto en sal HCl del producto no se determinó].

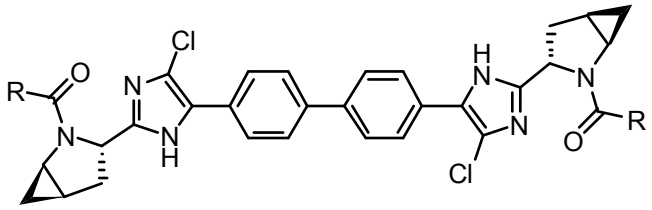
Ejemplo V3

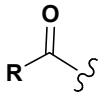
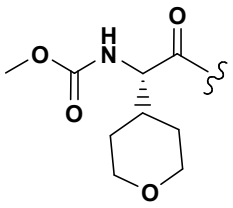
El Ejemplo V3 (sal en TFA) se preparó a partir de la sal HCl de pirrolidina V3a de acuerdo con el procedimiento descrito para la síntesis del ejemplo V1. RMN de ^{1}H (DMSO-d_6,= 2.5 ppm, 400 MHz): 12.59 (s muy ancho, ~2H), 7.86 (d, *J* =8.5, 4H), 7.80 (d, *J* = 8.3, 4H), 7.46 (app s ancho, 0.13H), 7.37 (d, *J* = 7.6, 1.73H), 6.97 (app s ancho, 0.14H), 4.97-4.94 (m, 2H), 4.52-4.35 (m, 2H), 3.63-3.45 (m, 8H), 2.36-2,23 (m, 4H), 1.96-1.83 (m, 2H), 1.82-1.67 (m, 2H), 1.64-1.49 (m, 2H), 1.13-0.82 (m, 8H), 0.78-0.61 (m, 2H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL (Cond. 1A): T_r = 2.66 min. CL/EM: Anal.

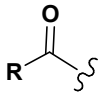
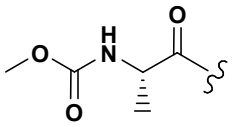
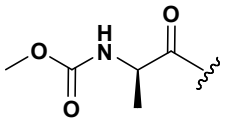
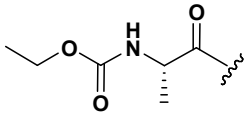
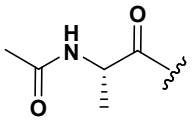
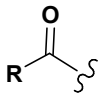
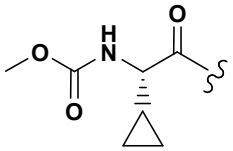
Calculado para $[M+H]^+$ $C_{40}H_{45}Cl_2N_8O_6$: 803.28; encontrado: 803.28.

Ejemplos V4-V6

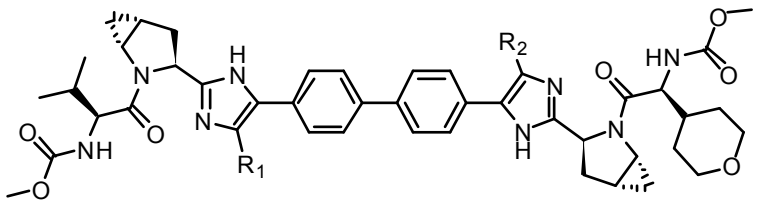
Los Ejemplos V4-V6 (sal en TFA) se prepararon a partir de la sal HCl de pirrolidina V3a y los ácidos adecuados de acuerdo con el procedimiento descrito para la síntesis del ejemplo V1.



Ejemplo		T_a (CL-Cond.); CL (Cond. 2a y 2b): Índice de homogeneidad en %; Datos de EM
V4		2.64 min (Cond. 1A); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{46}H_{53}Cl_2N_8O_8$: 915.34; encontrado: 915.70. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.63 (s muy ancho, ~2H), 7.87 (d, *J* = 8.6, 4H), 7.78 (d, *J* = 8.5, 4H), 7.42 (app s ancho, 0.1H), 7.26 (d, *J* = 8.6, 1.75H), 6.97 (app s ancho, 0.14H), 4.95 (dd, *J* = 8.4, 5.1, 2H), 4.48 (app t, *J* = 8.1, 2H), 3.85 (m, 4H), 3.73-3.64 (m, 2H), 3.54 (s, 6H), 3.32-3.18 (m, 4H), 2.37-2.19 (m, 4H), 2.05-1.91 (m, 2H), 1.91-1.78 (m, 2H), 1.71-1.58 (m, 2H), 1.56-1,39 (m, 4H), 1.39-1,25, (m, 2H), 1.05-0.93 (m, 2H), 0.77-0.66 (m, 2H)

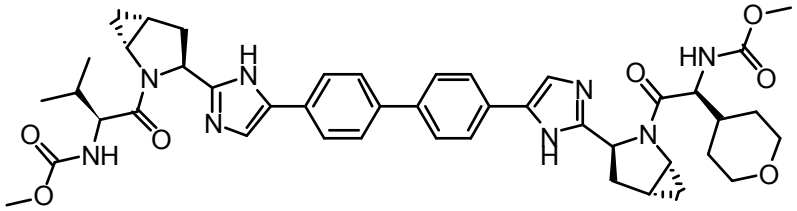
Ejemplo		T_a (CL-Cond.); CL (Cond. 2a y 2b): Índice de homogeneidad en %; Datos de EM
V5		2.59 min (Cond. 1A); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_6$: 775.25; encontrado: 775.29. RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.56 (s muy ancho, ~2H), 7.86 (d, *J* = 8.5, 4H), 7.80 (d, *J* = 8.5, 4H), 7.37 (d, *J* = 7.6, 1.70H), 7.02 (app s ancho, 0.3H), 4.95 (app t, *J* = 6.8, 2H), 4.63-4.54 (m, 2H), 3.62-3,34 ('m' y 's' solapados; s está en 3.52; 8H), 2.31-2,28 (m, 4H), 1.91-1.84 (m, 2H), 1.28 (s, 3H), 1.27 (d, *J* = 7, 6H), 1.02-0.97 (m, 2H), 0.76-0.61 (m, 2H).
V5.1		2.65 min (Cond. 1A); >95%; CL/EM: anal. calculado para $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_6$: 775.25; encontrado: 775.35.
V5.2		2.72 min (Cond. 1A); >95%; CL/EM: anal. calculado para $[M+H]^+$ $C_{40}H_{45}Cl_2N_8O_6$: 803.28; encontrado: 803.38.
V5.3		2.50 min (Cond. 1A); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{38}H_{41}Cl_2N_8O_4$: 743.26; encontrado: 743.36.
Ejemplo		Ta (CL-Cond.); CL (Cond. 2a y 2b): Índice de homogeneidad en %; Datos de EM
V6		2.75 min (V-Cond. 1); >95%; CL/EM: Anal. Calculado para [M+H]+ C42H45Cl2N8O6: 827.28; encontrado: 827.33.

Ejemplos V7 y V8



V7 (R_1 = H, R_2 = Cl)
V8 (R_1 = Cl, R_2 = H)

Ejemplo V7, Etapa a



A una solución de pirrolidina 1e/4HCl (0.350 g, 0.589 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0.103 g, 0.589 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (0.128 g, 0.589 mmol) y N,N-diisopropiletilamina (0.720 ml, 4.12 mmol) en DMF (3 ml)se añadió HATU (0.493 g, 1.295 mmol). La mezcla de reacción se agitó a ~25 °C durante 4 horas y después se diluyó con MeOH y se purificó mediante HPLC preparativa (Columna: XTERRA, 30 X 100 mm, S5; % inicial de B = 30, % final de B = 75; Tiempo de gradiente = 15 min; Tiempo de detención = 15 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de MeOH – 90% de H_2O – 0.1% de TFA; Disolvente de B = 90% de MeOH – 10% de H_2O – 0.1% de TFA), aislando el producto V7a de los tres posibles productos. El producto V7a se disolvió en MeOH y se lavó

eliminando las bases (cartucho de 6g MCX; lavado con MeOH; elución con NH_3/MeOH 2N) y se concentró *al vacío* dando un sólido marrón (103.2 mg). CL (Cond. 1A): T_r = 1.63 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_7$: 805.40; encontrado: 805.49.

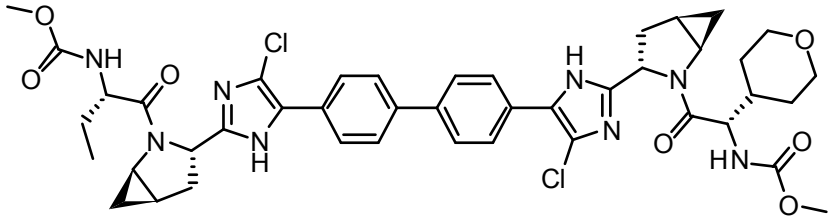
Ejemplos V7 y V8

Una solución del producto V7a (0.103 g, 0.128 mmol) y NCS (0.022 g, 0.167 mmol) en DMF (1.5 ml) se calentó a 50 °C durante 24 horas. Después de dejar enfriar hasta la temperatura ambiente, la mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (Columna: XTERRA, 30 X 100 mm, S5; % inicial de B = 40, % final de B = 100; Tiempo de gradiente = 15 min; Tiempo de detención = 17 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de MeOH – 90% de H_2O – 0.1% de TFA; Disolvente de B = 90% de MeOH – 10% de H_2O – 0.1% de TFA), aislando una mezcla de regioisómeros V7 y V8. La mezcla se disolvió en MeOH y se sometió a una diferente condición de purificación mediante HPLC preparativa (Columna: Waters-SunFire, 30 X 100 mm, S5; % inicial de B = 10, % final de B = 50; Tiempo de gradiente = 20 min; Tiempo de detención = 20 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de MeOH – 90% de H_2O – 0.1% de TFA; Disolvente B = 90% de acetonitrilo – 10% de H_2O – 0.1% de TFA), separando los dos regioisómeros en forma de sales en TFA. Ejemplo V7 (sólido blancuzco, 17.3

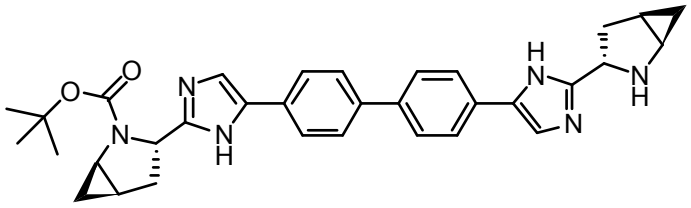
mg): RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.52 (app s ancho, demasiado ancho para integrar), 12.64 (app s ancho, demasiado ancho para integrar), 8.14 (s, 1H), 7.95-7.79 (m, 8H), 7.26 (dos 'd' solapadas, *J* = ~8.6, 1.70H), 7.10 (app s ancho, 0.08H), 6.98 (app s ancho, 0.22H), 5.01-4.97 (m, 1H), 4.96-4.92 (m, 1H), 4.50-4,46 (m, 1H), 4.43-4,40 (m, 1H), 3.90-3.81 (m, 2H), 3.79-3.72 (m, 1H), 3.71-3.64 (m, 1H), 3.54 (app s, 6H), 3.31-3.18 (m, 2H), 2.65-2.50 ('m' parcialmente solapado con disolvente, 1H), 2.45-2.19 (m, 3H), 2.18-2.08 (m, 1H), 2.04-1.89 (m, 2H), 1.89-1.79 (m, 1H), 1.69-1.59 (m, 1H), 1.55-1.41 (m, 2H), 1.38-1,23 (m,1H), 1.04-0.77 (m, 9H), 0.74-0.67 (m, 1H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL (Cond. 1a): T_r = 2.15 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{51}Cl_1N_8O_7$: 839.36; encontrado: 839.35. Ejemplo V8 (sólido blancuzco, 16.8 mg): RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 14.53 (s ancho, demasiado ancho para integrar), 12.61 (s ancho, demasiado ancho para integrar), 8.13 (s, 1H), 7.94 (d, *J* = 8.3, 2H), 7.90 (d, *J* = 8.6, 2H), 7.85 (d, *J* = 8.5, 2H), 7.82 (d, *J* = 8.6, 2H), 7.36 (d, *J* = 8.8, ~1H), 7.17 (d, *J* = 8.5, ~1H), 5.00-4.94 (m, 2H), 4.49 (app t, *J* = 7.7, 1H), 4.40 (app t, *J* = 7.9, 1H), 3.90-3.78 (m, 3H), 3.65-3.59 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 3.35-3.19 (m, 2H), 2.64-2.50 ('m' parcialmente solapado con señal de disolvente, 1H), 2.41-2.34 (m, 1H), 2.33-2,22 (m, 2H), 2.12-1.99 (m, 2H), 1.99-1.90 (m, 1H), 1.89-1.81 (m,

1H), 1.52-1,27 (m, 4H), 1.07-0.84 (m, 8H), 0.84-0.77 (m, 1H), 0.75-0.65 (m, 1H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL (Cond. 1a): T_r = 2.15 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{51}Cl_1N_8O_7$: 839.36; encontrado: 839.38.

Ejemplo V9.



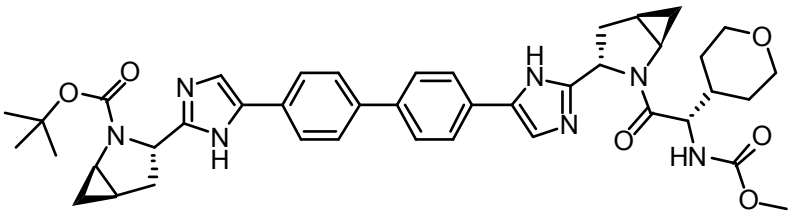
Ejemplo V9, Etapa a



A una mezcla de pirrolidina 1e/4HCl (2.00 g, 3.36 mmol) y Et_3N (2.3 ml, 16.82 mmol) en DMF (60 ml) se añadió Boc_2O (0.734 g, 3.36 mmol) seguido por DMAP (0.021 g, 0.168 mmol) y se agitó en condiciones ambientales durante 4.5 horas. El componente volátil se eliminó *al vacío* y el residuo se repartió entre NaOH 1.0N (20 ml) y 20% de $MeOH/CHCl_3$ (50 ml). La fase acuosa se lavó con 20% de $MeOH/CHCl_3$ (50 ml, 2x).). La fase orgánica combinada se secó ($MgSO_4$) y se concentró *al vacío*. A partir del material bruto resultante se preparó una malla de gel de sílice y se sometió a purificación en Biotage (160 g de gel de sílice) en el que

la columna se eluyó primero con EtOAc hasta la salida de toda la mancha de T_r superior (es decir, derivado de bis-Boc 1d; 0.28 g) y, después, la columna se eluyó con 5-10% de MeOH/CH_2Cl_2 en 2.5 l eluyendo bis-Boc x residual (seguido por mono-Boc V9a (0.81 g; ~que contiene 1.1 mol eq. de Et_3N). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{33}H_{37}N_6O_2$: 549.30; encontrado 549.45.

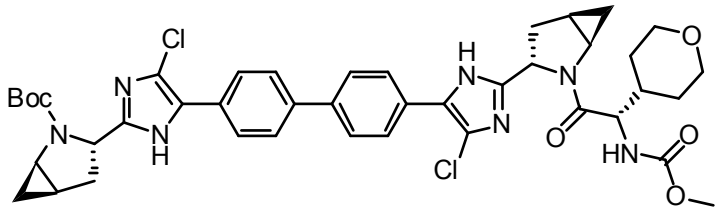
Ejemplo V9, Etapa b



A una solución de carbamato V9a (1 g, 1.823 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2*H*-piran-4-il)acético (0.400 g, 1.841 mmol) y N,N-diisopropiletilamina (0.65 ml, 3.72 mmol) en DMF (8 ml) se añadió HATU (0.770 g, 2.026 mmol) y la mezcla de reacción se agitó a ~25 °C durante 3 horas. El componente volátil se eliminó *al vacío* y el residuo se suspendió en 20% de MeOH/$CHCl_3$ (250 ml) se lavó con agua (3 x 40 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. El residuo se suspendió en $CHCl_3$ (4 ml) y se cargó en un cartucho de gel de sílice de Thomson y eluyó con 10% de MeOH/EtOAc, dando el producto V9b en forma de una espuma marrón (1.15 g). CL (V-Cond. 1): T_r = 1.70 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{50}N_7O_6$:

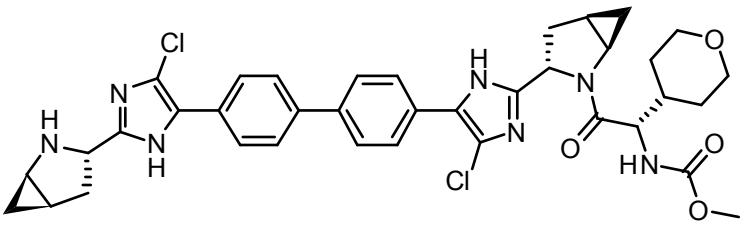
748.38; encontrado: 748.40.

Ejemplo V9, etapa c



Una solución de V9b (0.9387 g, 1.255 mmol) y NCS (0.335 g, 2.51 mmol) en DMF (13 ml) se calentó a 50 °C durante 24.5 h. El componente volátil se eliminó *al vacío* y el residuo se suspendió en CH_2Cl_2 (200 ml), se lavó con agua (3 x 50 ml), seguido por salmuera (50 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. El residuo se suspendió en CH_2Cl_2 (6 ml) y se sometió a purificación en gel de sílice (100% de acetato de etilo), dando el compuesto V9c en forma de un sólido amarillo (720.7 mg). CL (Cond. 1A): T_r = 3.19 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{48}Cl_2N_7O_6$: 816.30; encontrado: 816.35.

Ejemplo V9, etapa d



La pirrolidina V9d se preparó en forma de una sal HCl a partir de carbamato V9c de acuerdo con el

procedimiento descrito para la síntesis de V1b. RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.49-10.38 (m, 1H), 9.84-9.72 (m, 1H), 7.90-7.81 (m, 8H), 7.27 (d, *J* = 8.6, 0.89H), 6.99 (app s ancho, 0.11H), 4.98-4.95 (m, 1H), 4.65-4.55 (m, 1H), 4.50-4,46 (m, 1H), 3.90-3.80 (m, 2H), 3.76-3.64 (m, 1H), 3.54 (s, 3H), 3.41-3,32 (m, 1H), 3.32-3.19 (m, 2H), 2.54-2.40 ('m' parcialmente solapado con señal de disolvente, 2H), 2.36-2,24 (m, 2H), 2.06-1.95 (m, 1H), 1.94-1.78 (m, 2H), 1.69-1.57 (m, 1H), 1.55-1.40 (m, 2H), 1.39-1,27 (m,1H), 1.17-1.07 (m, 1H), 1.04-0.92 (m, 1H), 0.88-0.78 (m, 1H), 0.76-0.66 (m,1H). CL (Cond. 1a): T_a= 2.66 min; índice de homogeneidad > 95%. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{37}H_{40}Cl_2N_7O_4$: 716.25; encontrado: 716.28.

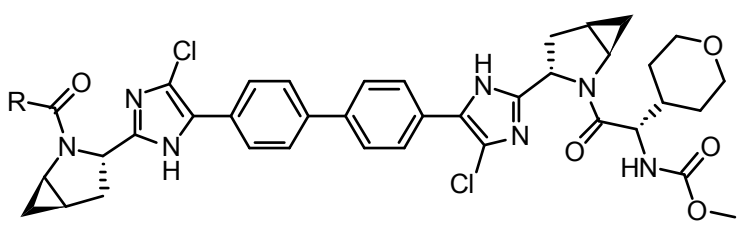
Ejemplo V9

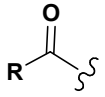
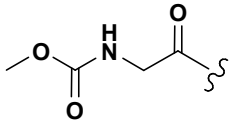
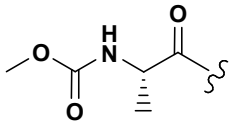
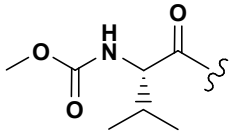
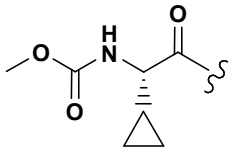
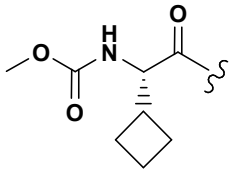
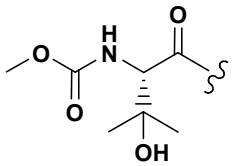
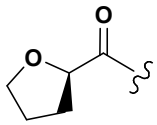
El Ejemplo V9 (sal en TFA) se preparó a partir de la sal HCl del intermedio V9d y ácido S)-2-(metoxicarbonilamino)butanoico de acuerdo con el procedimiento descrito para la síntesis del ejemplo V1. RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.59 (s ancho, ~2H), 7.87-7.77 (m, 8H), 7.29/7.26 (dos 'd' parcialmente solapados, *J* = 8.6/7.8, 1.82H), 6.97 (app s ancho, 0.18H), 4.97-4.93 (m, 2H), 4.50-4,42 (m, 2H), 3.90-3.81 (m, 2H), 3.72-3.65 (m, 1H), 3.60-

3.46 (m y dos s solapantes, los s están en 3.54 y 3.53, 7H), 3.32-3.18 (m, 2H), 2.38-2.18 (m, 4H), 2.05-1,23 (colección de 'm', 9H), 1.09-0.85 (m, 5H), 0.76-0.59 (m, 2H). CL (Cond. *2a y 2b*): índice de homogeneidad > 95%. CL (Cond. 1a): T_r = 2.66 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{43}H_{49}Cl_2N_8O_7$: 859.31; encontrado: 859.43.

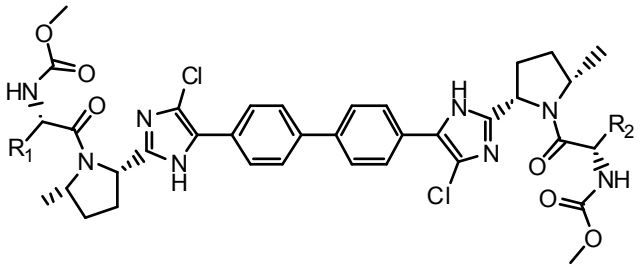
Ejemplos V10-V16

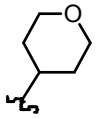
Los Ejemplos V10-V16 (sal en TFA) se prepararon a partir de la sal HCl de pirrolidina V9d y los ácidos adecuados de acuerdo con el procedimiento descrito para la preparación del Ejemplo V1. Los Ejemplos V13-16 requirieron una purificación HPLC de fase inversa adicional que empleó la condición siguiente: Columna: Waters-SunFire, 30 X 100 mm, S5; % inicial de B = 10, % final de B = 50; Tiempo de gradiente = 20 min; Tiempo de detención = 20 min; Caudal = 30 ml/min; Longitud de onda = 220; Disolvente A = 10% de acetonitrilo– 90% de H_2O – 0.1% de TFA; Disolvente B = 90% de acetonitrilo – 10% de H_2O – 0.1% de TFA.



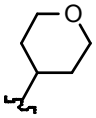
Ejemplo		T_a (CL-Cond.); CL (Cond. 2a y 2b): Índice de homogeneidad en %; Datos de EM
V10		2.59 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{41}H_{45}Cl_2N_8O_7$: 831.28; encontrado: 831.31.
V11		2.54 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{47}Cl_2N_8O_7$: 845.29; encontrado: 845.17.
V12		2.69 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{51}Cl_2N_8O_7$: 873.33; encontrado: 873.27.
V13		2.73 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{49}Cl_2N_8O_7$: 871.31; encontrado: 871.41.
V14		2.83 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{45}H_{51}Cl_2N_8O_7$: 885.33; encontrado 885.45.
V15		2.70 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{51}Cl_2N_8O_8$: 889.32; encontrado 889.44.
V16		2.52 min (Cond. 1a); >95%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{46}Cl_2N_7O_6$: 814.29; encontrado 814.18.

Ejemplos GW1-1 a GW1-3



$R_1 = R_2 =$ 

Ejemplo GW1-1

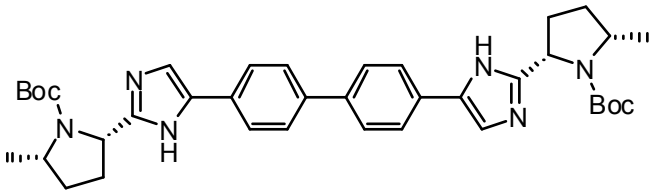
$R_1 =$  $R_2 =$ 

Ejemplo GW1-2

$R_1 = R_2 =$ 

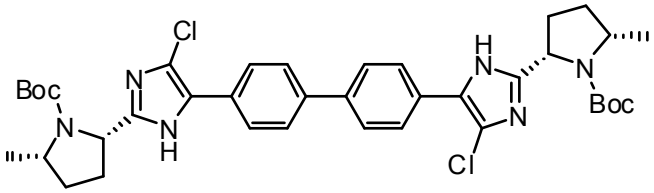
Ejemplo GW1-3

Ejemplo GW1, Etapa a



Para la preparación del carbamato GW1a, véase la solicitud de patente US 2009/0068140.

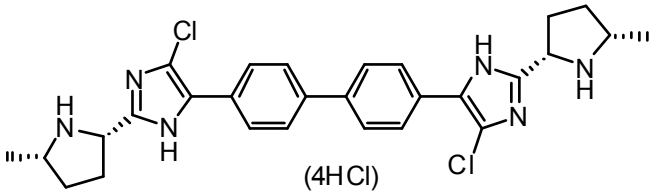
Ejemplo GW1, Etapa b



A una solución de carbamato GQ1a (0.830 g, 1.271 mmol) en DMF (9 ml) se añadió NCS (0.221 g, 1.653 mmol). La mezcla de reacción se calentó a 50 °C durante 16 horas. Se añadió más NCS (0.1 g, 0.75 mmol) y el calentamiento continuó durante 4 horas. Se dejó enfriar hasta la temperatura ambiente y se repartió entre DCM y agua (20 ml de cada). La capa acuosa se extrajo con DCM (20 ml) y la fase orgánica

combinada se secó (Na_2SO_4) y se concentró al vacío. El material bruto resultante se disolvió en MeOH y se sometió a purificación mediante HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) recuperando las sales en TFA de GW1b en forma de una espuma amarilla (0.25 g). RMN de ^1H (MeOD, δ = 3.30 ppm, 400 MHz): 7.82 (app s, 8H), 4.95-4.85 ('m' parcialmente solapada con señal HOD, 2H), 4.04 (m, 2H), 2.36-2.14 (m, 6H), 1.77 (m, 2H), 1.50-1,20 (solapamiento de 's ancho' y 'd', 24H). CL (Cond. Ia): TR = 3.0 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{38}H_{47}Cl_2N_6O_4$: 721.30; encontrado 721.32.

Ejemplo GW1, Etapa c



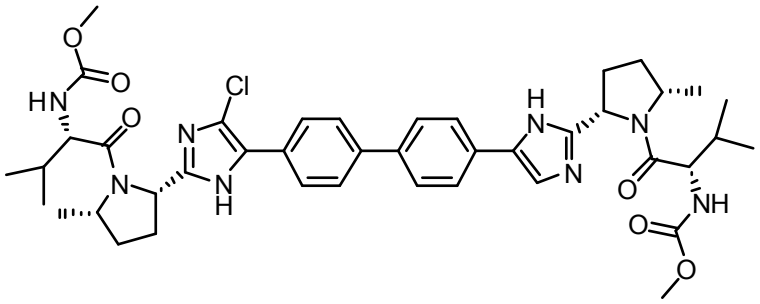
Al carbamato GW1b (0.29 g, 0.306 mmol) se añadió HCl 4N en dioxano (10 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. El disolvente se eliminó y se secó al vacío durante la noche, dando la sal HCl del producto GW1c en forma de un sólido marrón (0.21g). RMN de ^1H (MeOD, δ = 3.30 ppm, 400 MHz): 7.85 (d, *J* = 8.6, 4H), 7.80 (d, *J* = 8.8, 4H), 4.95-4.85 (m, 2H), 3.89-3.80 (m, 2H), 2.58-2.31 (m, 6H), 2.01-1.91 (m, 2H), 1.50 (d, 6.5 Hz, 6H). CL (Cond. 1A): TR = 3.0 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{28}H_{31}Cl_2N_6$: 521.20; encontrado 521.20.

Ejemplos GW1-1 a GW1-3

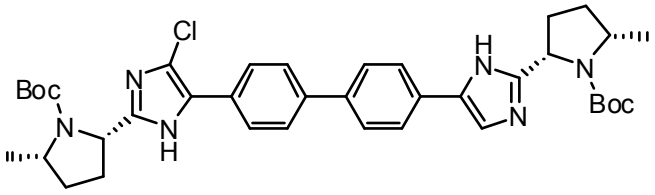
A una solución de la sal HCl de GW1c (150 mg, 0.225 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (57.6 mg, 0.265 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (48.0 mg, 0.274 mmol) en DMF (10 ml) se añadió DIEA (0.236 ml, 1.349 mmol) y HATU (176 mg, 0.463 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) aislando los tres productos en forma de sales en TFA. El Ejemplo GW1-1 (espuma amarillo claro, 25 mg) se contaminó con impurezas no identificadas. RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 8.05-7.93 (m, 1.54H), 7.87-7.56 (m, 6.46H), 5.42 (d ancho, *J* = 6.6, 0.68H), 4.97 (m, 1.32H), 4.76-4.69 (m, 1.2H), 4.31-4.14 (m, 2.8H), 3.98-3.84 (m, 4H), 3.68/3.67/3.63 (tres 's', 6H), 3.40-3.21 ('m' parcialmente solapado con señal de disolvente, 4H), 2.72 (m, 0.7H), 2.45-1.14 (solapado con muchos 'm' y dos 'd', 'd' en 1.51 y 1.18 con *J* = 6.5 y 6.3, respectivamente; 23.3H). CL (Cond. 2a y 2b): índice de homogeneidad > 91.8%. CL (Cond. 1c): TR = 6.22 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{46}H_{57}Cl_2N_8O_8$: 919.37; encontrado 919.9. Ejemplo GW1-2 (espuma amarillo claro, 39 mg); CL (Cond. 2a y 2b): índice de homogeneidad > 95%. CL (Cond.

1A): TR = 2.97 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{55}Cl_2N_8O_7$: 877.36; encontrado 877.35. Ejemplo GW1-3 (espuma amarillo claro, 22 mg), CL (Cond. 2a y 2b): índice de homogeneidad > 95%. CL (Cond. 1A): TR = 3.07 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; encontrado 835.34.

Ejemplo GW2



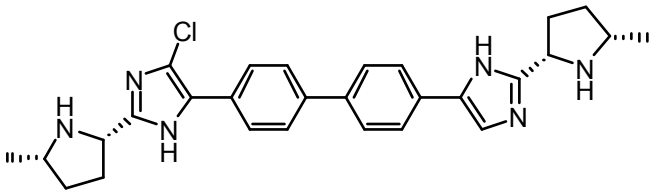
Ejemplo GW2, Etapa a



A una solución de carbamato GW1a (0.830 g, 1.271 mmol) en DMF (9 ml) se añadió NCS (0.221 g, 1.653 mmol). La mezcla de reacción se calentó a 50 °C durante 16 horas. Se añadió NCS adicional (0.1g, 0.75 mmol) y el calentamiento continuó a 50°C durante 4 horas adicionales. La mezcla se repartió entre DCM y agua (20 ml de cada). La fase acuosa se extrajo con DCM (20 ml) y la fase combinada se secó con Na_2SO_4 y se concentró *al vacío*. El producto bruto resultante se disolvió en MeOH y se sometió a purificación mediante HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X

100 mm S10 Axia) recuperando el carbamato GW2a en forma de una espuma amarillo claro (0.03g). RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.76-7.64 (m, 8H), 7.34 (s, 1H), 5.10-4.65 (solapante con la señal HOD, m, 2H), 3.99 (m, 2H), 2.31-2.01 (m, 6H), 1.78-1.76 (m, 2H), 1.55-1.15 (app m ancho, 24H). CL (Cond. 1A): TR = 2.55 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{38}H_{48}ClN_6O$: 687.34; encontrado 687.39.

Ejemplo GW2, Etapa b



Al carbamato GW2a (0.19 g, 0.208 mmol) se añadió HCl 4N en dioxano (10 ml) y se agitó a temperatura ambiente durante 4 horas. Se eliminó el disolvente y se secó al vacío durante la noche, dando la san HCl de la pirrolidina GW2b en forma de un sólido marrón (0.16g). RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 8.11 (s, 1H), 7.95 (d, *J* = 8.5, 2H), 7.87 (aparece 'd', 4H), 7.82 (d, *J* = 8.8, 2H), 5.22 (m, 1H), 4.92 – 4.83 (solapante con la señal HOD, m, 1H), 3.99 (m, 1H), 3.84 (m, 1H), 2.78-2.62 (m, 2H), 2.57-2.31 (m, 4H), 2.12-1.91 (m, 2H), 1.55 (d, *J* = 6.8, 3H), 1.50 (d, *J*= 6.8, 3H). CL (Cond. Ia): TR = 1.74 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{28}H_{32}ClN_6$: 487.24; encontrado 487.21.

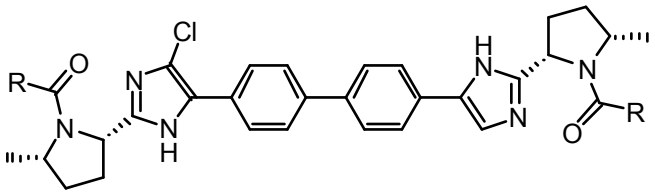
Ejemplo GW2

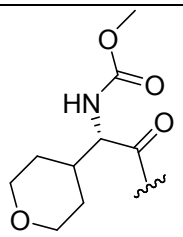
A una solución de la sal HCl de la pirrolidina GW2b

(80 mg, 0.126 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (48.7 mg, 0.278 mmol) en DMF (5 ml) se añadieron DIEA (0.132 ml, 0.758 mmol) y HATU (99 mg, 0.260 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) recuperando las sales en TFA de GW2 en forma de una espuma amarilla (50 mg). RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 8.00-7.75 (m, 9H), 5.71 (app m ancho, 0.2H), 5.40 (d, *J* = 6.3, 0.45 H), 5.15-5.11 (m, 0.87H), 5.00-4.96 (m, 0.92H), 4.81-4.68 (m, 1.56H), 4.26-4.03 (m, 2H), 3.71/3.70/3.64/3.63 (cuatro 's', 6H), 2.77-1.87 (m, 9.24H), 1.65-1.48 ('m' & 'd' solapados, 4.66 H), 1.28 (d, *J* = 0.62H), 1.17 (d, *J* = 6.3H, 1.23H), 1.06-0.82 (m, 12.15H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. CL/EM (Cond. 1A): TR = 2.46 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{54}ClN_8O_5$: 801.39; encontrado 801.41.

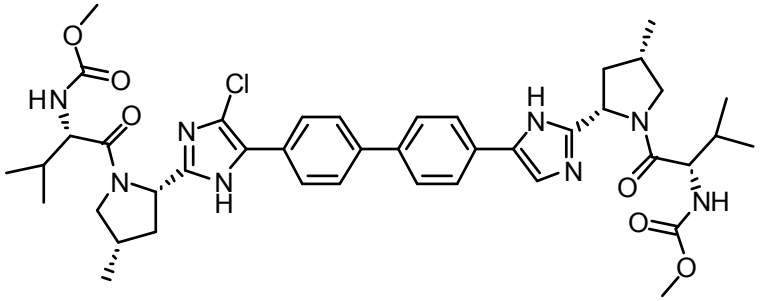
Ejemplo GW2-1.

El Ejemplo GW2-1 (sal en TFA) se preparó a partir de la pirrolidina GW2b y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2.

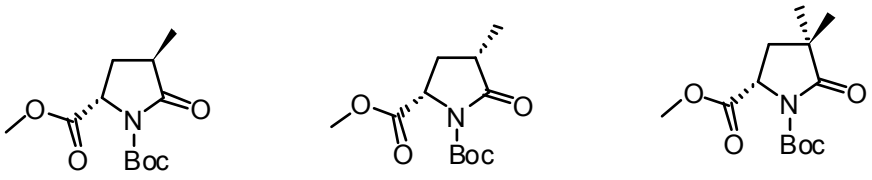


Ejemplo		TR (CL-Cond.); % índice de homogeneidad; datos de EM
GW2-1		2.23 min (Cond. 1A); >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{46}H_{58}ClN_8O_8$: 885.41; encontrado 885.37

Ejemplo GW3



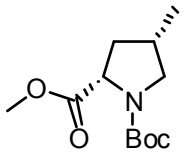
Ejemplo GW3, Etapa a



GW3a-1 GW3a-2 GW3a-3

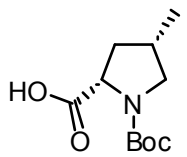
Los tres ésteres anteriores se prepararon a partir de 5-oxopirrolidin-1,2-dicarboxilato de (S)-1-*terc*-butil 2-metilo de acuerdo con el procedimiento descrito en *Tetrahedon Letters*, 2003, 3203-3205.

Ejemplo GW3, Etapa b



Se añadió complejo de borano-sulfuro de metilo (5.44 ml, 10.88 mmol) a una solución del éster GW3a-2 (1.4 g, 5.44 mmol) en THF (25 ml) y la mezcla de reacción se calentó a 40 °C durante 7 horas. El componente volátil se eliminó *a vacío* y el residuo se fraccionó entre EtOAc y agua (50 ml cada uno). La capa acuosa se extrajo con EtOAc (30 ml) y la fase orgánica combinada se secó con Na_2SO_4, y se concentró *al vacío*. El aceite incoloro resultante se purificó con una cromatografía ultrarrápida (0-50% de EtOAc/hexano) proporcionando el éster GW3b en forma de un aceite incoloro (0.77 g). RMN de ^1H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.29-4.18 (m, 1H), 3.78-3.66 (m, 4H), 2.99 (app t, *J* = 10.1, 1H), 2.43-2.97 (m, 1H), 2.43-2.37 (m, 1H), 2.30-2.18 (m, 1H), 1.60-1.52 (m, 1H), 1.47/1.42 (dps 's', 9H), 1.08-1.05 (m, 3H).

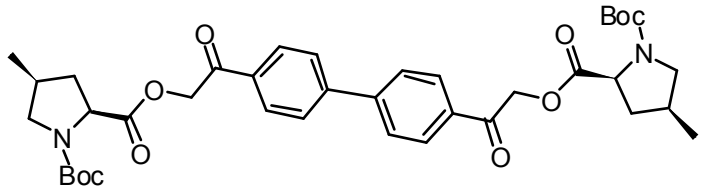
Ejemplo GW3, Etapa c



A una solución del éster GW3b (1.69 g, 6.95 mmol) en etanol (10 ml) se añadió solución de LiOH (0.250 g, 10.42

mmol) en agua (5.00 ml), y la mezcla de reacción se agitó a temperatura ambiente durante 5 horas. El disolvente orgánico se evaporó *a vacío* y el residuo se diluyó con agua (10 ml) y se lavó con éter (10 ml). Se enfrió en un baño de agua y hielo, y se acidificó a un intervalo de pH de ~2 con HCl 1 N. Después se extrajo con EtOAc (20 ml, 3x). La capa orgánica se secó con Na_2SO_4 y se concentró *a vacío* dando el ácido GW3c en forma de un aceite incoloro, que se convirtió en un sólido blanco tras la exposición extendida a alto vacío (1.38g). RMN de ^1H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.39-4.22 (m, 1H), 3.80-3.69 (m, 0.91H), 3.59-3,35 (m, 0.18H), 3.03-2.89 (m, 0.91H), 2.51-2,22 (m, 2H), 1.98-1.91 (m, 0.71H), 1.68-1.60 (0.29H), 1.50/1.44 (dos 's', 9H), 1.09 (app m, 3H).

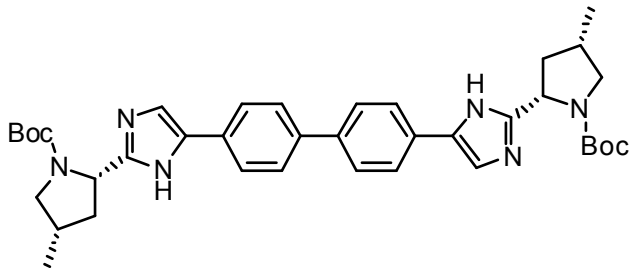
Ejemplo GW3, Etapa d



A una suspensión del GW3c (1.83 g, 7.98 mmol) y 1.1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (1.581 g, 3.99 mmol) en CH_3CN (30 ml) se añadió DIEA (1.436 ml, 8.22 mmol) y la mezcla se agitó a temperatura ambiente durante 4 horas. El disolvente se eliminó *al vacío* y el residuo se repartió entre EtOAc y agua (50 ml de cada uno). La fase orgánica se lavó con $NaHCO_3$ saturado (20 ml), se secó con Na_2SO_4 y se concentró *al vacío*, proporcionando el diéster GW3d en forma

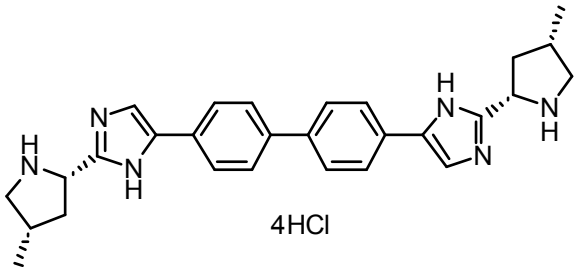
de un sólido amarillo (2.67g), que se usó como tal en la siguiente etapa.

Ejemplo GW3, Etapa e



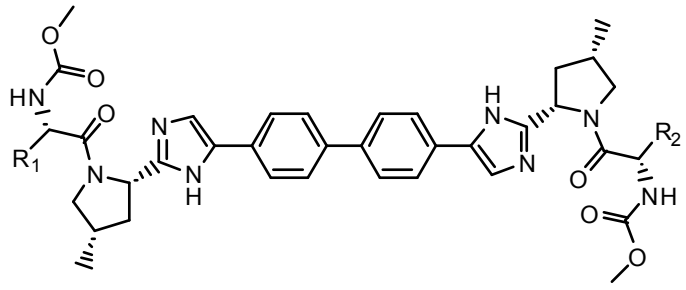
A una solución del dicetoéster GW3d (2.67 g, 3.85 mmol) en xilenos (30 ml) se añadió acetato amónico (2.97 g, 38.5 mmol) y la mezcla se calentó a 140°C durante 6 horas en un tubo sellado. El componente volátil se eliminó *a vacío* y el residuo se fraccionó entre DCM (50 ml) y agua (50 ml). La capa orgánica se lavó con $NaHCO_3$ saturado (20 mL), se secó con Na_2SO_4 y se concentró *al vacío*. El material bruto resultante se purificó con una cromatografía ultrarrápida (50-100% de EtOAc/hexano, 100% de EtOAc-10% de MeOH/EtOAc) dando el imidazol GW3 en forma de un sólido naranja (1.3g). RMN de ^1H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21-11.87 (tres s anchos, 2H), 7.82-7.51 (m, 9.2H), 7.30 (m, 0.6H), 6.88-6.81 (m, 0.2H), 4.9-4.67 (m, 1.81H), 3.98-3.93 (m, 0.19H), 3.77-3.54 (m, 2H), 3.07-2.76 (m, 2H), 2.43-2.04 (m, 4H), 1.80-1.56 (m, 2H), 1.41-1,33 (m, 8H), 1.10-1.04 (m, 16H). CL/EM (Cond. 1A): TR = 2.09 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; encontrado 653.51.

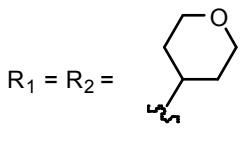
Ejemplo GW3, Etapa f



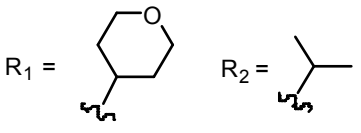
Se añadió HCl N en dioxano (12.10 ml, 48.4 mmol) al carbamato GW3e (1.3 g, 1.99 mmol) y la mezcla se agitó a temperatura ambiente durante 5 horas. El componente volátil se eliminó *al vacío* y el producto se secó al vacío durante la noche, dando la sal HCl de la pirrolidina GW3f en forma de un sólido amarillo (1.14g). RMN de ^{1}H (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.32 (app s ancho, 2H), 9.79 (app s ancho, 2H), 8.13 (s, 2H), 8.02 (d, *J*=8.3, 4H), 7.99 (d, *J*=8.3, 4H), 5.01 (m ancho, 2H), 3.47 (m ancho, 2H), 3.05 (m ancho, 2H), 2.62 (m, 2H), 2.45 (m, 2H), 2.21 (m, 2H), 1.13 (d, *J* = 6.3, 6H). CL/EM (Cond. 1A): TR = 2.09 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{28}H_{33}N_6$: 453.28; encontrado 453.17.

Ejemplo GW3, Etapa g

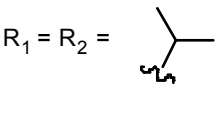




(GW3g-1)



(GW3g-2)



(GW3g-3)

A una suspensión de la sal HCl de pirrolidina GW3f

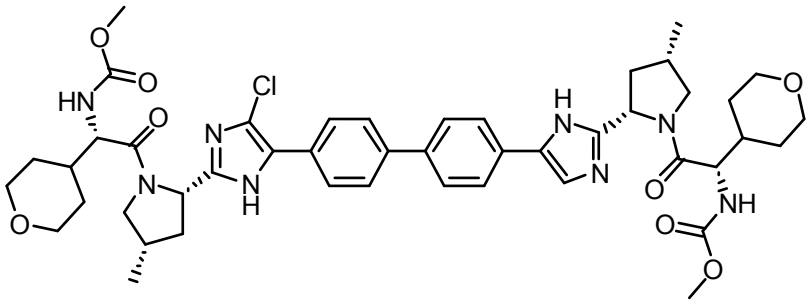
(1.14 g, 1.905 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (0.488 g, 2.248 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0.407 g, 2.324 mmol) en DMF (15 ml) se añadió DIEA (1.996 ml, 11.43 mmol). Se efectuó una disolución total con la ayuda de sonicación y después se añadió HATU (1.478 g, 3.89 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) dando las sales en TFA de tres productos: GW3g-1 (0.28g), GW3g-2 (0.64g) y GW3g-3 (0.36g) en forma de una espuma amarillo claro. Producto GW3g-3: RMN de ^{1}H (DMSO, δ = 2.5 ppm, 400 MHz): 14.74 (app s ancho, no integrable), 8.16 (s, 2H), 7.97 (d, *J*=8.6, 4H), 7.88 (d, *J*=8.3, 4H), 7.29 (d, *J*=8.0, < 2H), 5.23 (m ancho, 0.1H), 5.07 (dd, *J* = 10.6, 7, 1.9H), 4.18 (m, 2H), 4.09 (m, 2H), 3.53 (s, 6H), 3.39 (m, 2H), 2.56-2.35 ('m' parcialmente solapado con señal de disolvente, 2H), 1.95 (m, 2H), 1.82 (m, 2H), 1.13 (d, *J*=6.3, 6H), 0.79 (d, *J*=6.5, 6H), 0.76 (d, *J*=6.5, 6H) [Note: las últimas tres integraciones incluyen rotámeros minoritarios con señales en la región de 1.1-0.85 ppm de que tenían picos]. CL/EM (Cond. 1A): TR = 1.79 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; encontrado 767.30. Producto GW3g-1, CL/EM (Cond. Ia): TR =

1.62 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{46}H_{59}N_8O_8$: 851.45; encontrado 851.33. Producto GW3g-2, CL/EM (Cond. 1A): TR = 1.70 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{57}N_8O_7$: 809.44; encontrado 809.30.

Ejemplo GW3

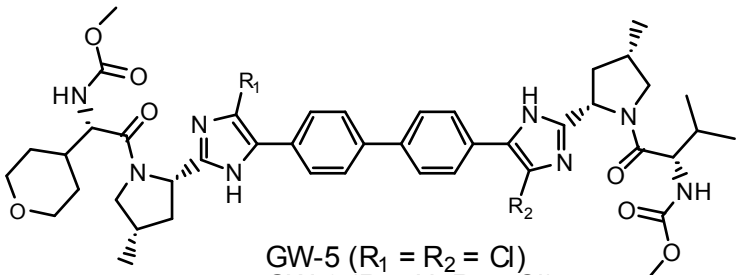
A una solución de GW3g-3/2TFA (160 mg, 0.174 mmol) en DMF (2 ml) se añadió NCS (30.6 mg, 0.229 mmol). La mezcla se calentó a 50 °C durante 5.5 horas. El residuo se disolvió en MeOH y se sometió a purificación mediante HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) recuperando las sales en TFA de GW3 en forma de una espuma amarilla (40 mg). [Nota: para los casos análogos, la cloración se realizó en un material de partida que estaba en forma de una base libre.] RMN de ^1H (MeOD, δ = 3.30 ppm, 400 MHz): 7.88 (s, 1H), 7.84-7.76 (m, 8H), 5.19 (dd, *J* = 11.1, 7.1, 1H), 4.98 (dd, *J* = 10.4, 7.3, 1H), 4.32 (m, 1H), 4.24-4.17 (m, 3H), 3.63 (s, 3H), 3.62 (s, 3H), 3.40-3,33 (m, 2H), 2.65 (m, 1H), 2.50 (m, 2H), 2.37 (m, 1H), 1.99 (m, 2H), 1.82 (m, 2H), 1.22 (d, *J*=6.3, 2.85H), 1.18 (d, *J*=6.3, 2.85H), 1.09 (m, 0.3H), 0.92-0.85 (m, 12H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. CL/EM (Cond. Ia): TR = 2.32 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{54}ClN_8O_6$: 801.39; encontrado 801.25.

Ejemplo GW4



El Ejemplo GW4 (sal en TFA) se preparó a partir de GW3g-1 de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW3. CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TA= 2.17 min (Cond. 1A). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{46}H_{58}ClN_8O_8$: 885.41; encontrado 885.26.

Ejemplos GW5 a GW7



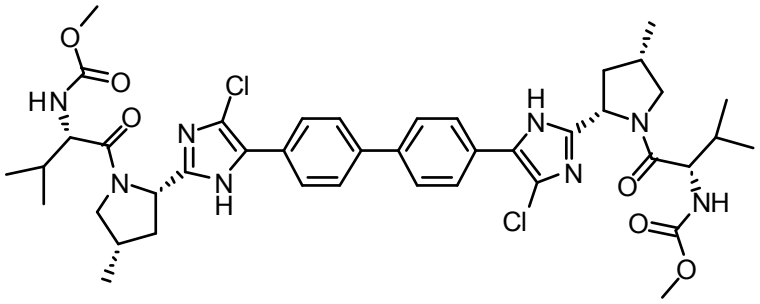
GW-5 (R_1 = R_2 = Cl)
GW-6 (R_1 =H, R_2 = Cl)
GW-7 (R_1 = Cl, R_2 = H)

A una solución GW3g-2 (565 mg, 0.588 mmol) en DMF (2 ml) se añadió NCS (0.021 g, 0.161 mmol) y la mezcla de reacción se calentó a 50°C durante 17 horas. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30X100 mm S10 Axia) dando dos fracciones (una es GW5 y la segunda es

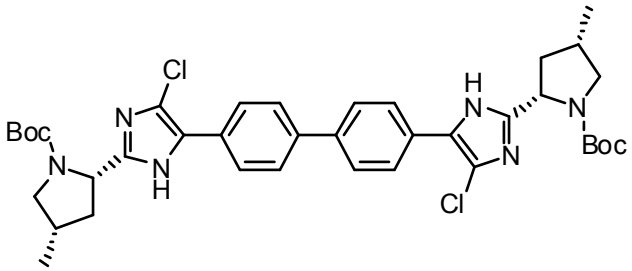
una mezcla de GW6 y GW7). Las fracciones se secaron *al vacío* y se recuperaron en forma de un sólido amarillo claro. Ambas fracciones se disolvieron por separado en metanol y se sometieron a purificación en HPLC de fase inversa (ACN/TFA/Agua, Water-Sunfire 30X100 mm S5) recuperando las sales en TFA del Ejemplo GW5, GW6 y GW7. Ejemplo GW5: RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.74 (m, 8H), 5.02 (m, 2H), 4.29-4.18 (m, 4H), 3.90 (m, 2H), 3.63 (s, 6H), 3.41-3,33 (m, 4H), 2.52 (m, 2H), 2.39 (m ancho, 2H), 2.01-1.79 (m, 4H), 1.58-1,27 (m, 4H), 1.18 (d, *J*=6.5, 5.63H), 1.09 (m, 0.37H), 0.93 (d, *J*=6.8, 3H), 0.88 (d, *J*=6.5, 3H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. 1A): TR = 2.81 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{55}Cl_2N_8O_7$: 877.36; encontrado 877.30. Ejemplo GW6: RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.86 (s, 1H), 7.82-7.73 (m, 8H), 5.19 (dd, *J* = 11, 7, 1H), 4.98 (dd, *J* = 10.4, 7.3, 1H), 4.33-4.19 (m, 4H), 3.90 (m, 2H), 3.67 (m, 0.35H), 3.63/3.62 (dos 's' solapados, 5.65H), 3.41-3,31 (m, 4H), 2.65 (m, 1H), 2.49 (m, 2H), 2.38 (m, 1H), 2.00-1.79 (m, 4H), 1.57-1,27 (m, 4H), 1.22/1.18 dos 'd' solapantes, *J* = 6.5/6.3, respectivamente, 5.69H), 1.09 (m, 0.31H), 0.90/0.86 (dos 'd' solapantes, *J* = 6.8/6.8, 6H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TR = 2.25 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{56}ClN_8O_7$: 843.40; encontrado 843.24. Ejemplo GW7: RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.87-

7.75 (m, 9H), 5.19 (dd, *J*= 11, 7.0, 1H), 4.99 (dd, *J* = 10.3, 7.3, 1H), 4.38-4.17 (m, 4H), 3.90 (m, 2H), 3.64/3.62 (dos 's', 6H), 3.41-3.26 ('m' parcialmente solapada con señal de disolvente, 4H), 2.64 (m, 1H), 2.50 (m, 2H), 2.37 (m, 1H), 2.03-1.79 (m, 4H), 1.60-1.08 (m, 10H), 0.92 (d, *J*=6.8, 3H), 0.86 (d, *J*=6.8, 3H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. 1A): TR = 2.24 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{56}ClN_8O_7$: 843.40; encontrado 843.24.

Ejemplo GW8



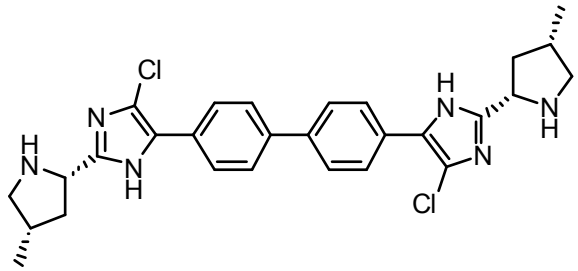
Ejemplo GW8, Etapa a



A una solución GW3e (0.360 g, 0.551 mmol) en DMF (9 ml) se añadió NCS (0.096 g, 0.717 mmol) y la mezcla de reacción se calentó a 50°C durante 15 horas. El residuo se diluyó con MeOH y se sometió a purificación mediante HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X

100 mm S10 Axia) recuperando la sal en TFA de GW8a en forma de una espuma amarillo claro (20 mg). También se aislaron las sales en TFA de GW3e (60 mg) y el análogo mono-cloro (70 mg). Carbamato GW8a: RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.83 (app s, 8H), 4.95-4.79 ('m' parcialmente solapado con señal HOD, 2H), 3.85-3.75 (m, 2H), 3.14 (m, 2H), 2.58-2.48 (m, 2H), 2.44-2.30 (m, 2H), 1.80-1.71 (m, 2H), 1.43 (s, 6H), 1.23 (s, 12H), 1.14/1.12 (dos 's' solapantes, 6H). EM/CL (Cond. Ia): TR = 2.98 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{38}H_{47}ClN_6O_4$: 721.30; encontrado 721.39.

Ejemplo GW8, Etapa b



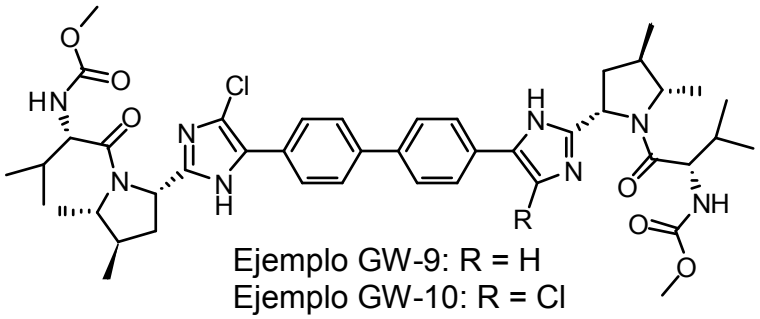
Se añadió HCl 4N en dioxano (3 ml) a la sal en TFA de GW8a (55 mg, 0.063 mmol) y la mezcla se agitó a temperatura ambiente durante 5 horas. Se eliminó el disolvente *al vacío* y el residuo se secó al vacío durante la noche, dando la sal HCl de la pirrolidina GW8b en forma de un sólido marrón (50 mg). EM/CL (Cond. Ia): TR = 2.20 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{28}H_{31}Cl_2N_6$: 521.20; encontrado 521.20.

Ejemplo GW8

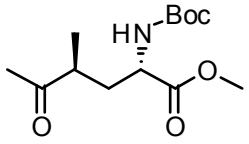
A una suspensión de la sal HCl de GW8b (50 mg,

0.075 mmol) en DMF (3 ml) se añadieron ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (28.9 mg, 0.165 mmol), DIEA (0.079 ml, 0.450 mmol) y HATU (58.7 mg, 0.154 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) recuperando las sales en TFA de GW8 en forma de una espuma amarilla (40 mg). RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.80-7.75 (m, 8H), 5.01 (dd, *J* = 10.4, 7.4, 2H), 4.26-4.17 (m, 4H), 3.63 (s, 6H), 3.38-3,33 (m, 2H), 2.52-2.49 (m, 2H), 2.45-2.33 (m, 2H), 2.03-1.95 (m, 2H), 1.87-1.79 (m, 2H), 1.19 (d, *J*=6.3, 6H), 0.92 (d, *J*=6.8, 6H), 0.87 (d, *J*=6.8, 6H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TR = 2.89 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; encontrado 835.41.

Ejemplos GW9 y GW10



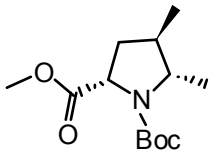
Ejemplo GW9, Etapa a



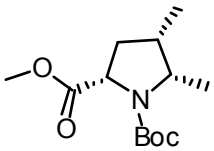
A una solución GW3a-2 (1.31 g, 5.09 mmol) en THF

(25 ml) se añadió bromuro de metilmagnesio (2.037 ml, 6.11 mmol) gota a gota a -40°C (baño de hielo seco/acetona). Se agitó a la misma temperatura durante 2 horas y, después, se retiró el baño y se continuó agitando durante 2 hora adicional. Se añadieron ácido acético (1 ml), agua (10 ml) y éter (50 ml), la mezcla se agitó y la capa orgánica se separó. La capa orgánica se lavó con agua, se secó sobre Na_2SO_4 y se concentró *a vacío*. El material en bruto resultante se purificó con cromatografía ultrarrápida (5-95% de EtOAc/hexano) proporcionando el éster GW9 en forma de un aceite incoloro (0.6 g). RMN de ^1H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.97 (br d, *J* = 8.3, 1H), 4.29 (m, 1H), 3.74/3.73 ('s' solapante, 3H), 2.66 (m, 1H), 2.27-2,22 (m, 0.21H), 2.17 (s, 2.58H), 2.10-2.02 (m, 1.22H), 1.80-1.1.74 (m, 1H), 1.43/1.40 ('s' solapante, 9H), 1.16 (d, *J*=7.1, 2.6H), 1.05(d, *J*=6.8, 0.4H).

Ejemplo GW9, Etapa b



GW-9b-1



GW-9b-2

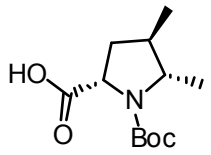
A una solución de la cetona GW9a (0.6 g, 2.195 mmol) en DCM (15 ml) se añadió TFA (0.849 ml, 10.98 mmol) y la mezcla se agitó a temperatura ambiente durante 7 horas. El componente volátil se eliminó *al vacío* y se secó al vacío durante la noche, dando un aceite amarillo claro (0.63 g).

Una solución del producto bruto anterior (0.5g, 1.8 mmol) en metanol (20 ml) se añadió a un frasco agitador Parr de 500 ml que contiene Pd/C (0.025 g, 0.234 mmol). Después se procedió a evacuar y volver a cargar con nitrógeno (3 veces), la mezcla se agitó a 345 kPa durante 24 horas. La mezcla de reacción se filtró a través de un papel de filtro y el componente volátil se eliminó *al vacío*, proporcionando un aceite amarillo claro (0.41g).

A una solución del producto bruto anterior (0.48g, 1.77 mmol) en CH_2Cl_2 (7 mL) se añadió DMAP (10.81 mg, 0.088 mmol), trietilamina (0.740 ml, 5.31 mmol). Se añadió dicarbonato de di-terc-butilo (0.386 g, 1.77 mmol) en porciones durante 15 minutos y la mezcla se agitó a temperatura ambiente durante 18 horas. Después de eliminar el componente volátil *al vacío*, el material en bruto se purificó con cromatografía ultrarrápida (0-22% de EtOAc/hexano) proporcionando dos productos mayoritarios. El primer eluido fue GW9b-1 (0.54g).. RMN de ^1H ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.41/4.30 (m ancho, 1H), 3.74 (s, 3H), 3.48/3.33 (m ancho, 1H), 2.37-2,22 (m, 0.2H), 2.10-2.04 (m, 0.9H), 1.98-1.19 (m, 0.9H), 1.79 (m, 1H), 1.46-1,32 (m, 12H), 1.05/1.01/0.97 (tres 'd' solapantes, *J* = 6.8/6.6/6.3, respectivamente, 3H). El segundo eluido fue GW9b-2 contaminado con impurezas no identificadas (0.48 g).. Las fracciones transparentes de GW9b-2 se usaron para adquirir

los datos de espectro siguientes: RMN de ^1H ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.23-4.12 (dos 'dd' solapantes, 1H), 4.00-3.85 (dos 'm' solapantes, 1H), 3.72/3.71 ('s' solapante, 3H), 2.34-2,20 (m, 2H), 1.69-1.55 (1H), 1.45/1.39 ('s' solapante, 9H), 1.13-1.01 (m, 3.13H), 0.97 (d, *J* = 6.3, 2.87H).

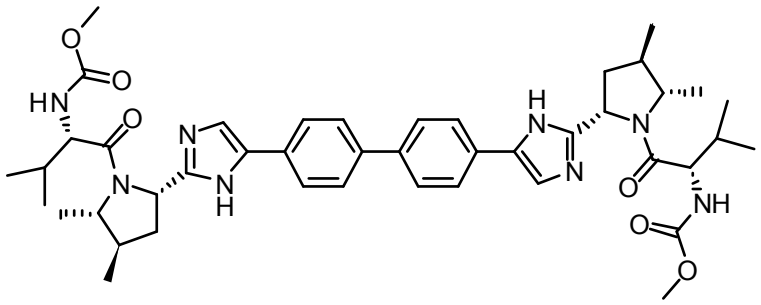
Ejemplo GW9, Etapa c



A una solución de GW9b-1 (3.73 g, 14.50 mmol) en etanol (40 ml) se añadió solución de LiOH (0.417 g, 17.39 mmol) en agua (20.00 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 6 horas. Se añadió más LiOH (0.1g, 4.3 mmol) y el calentamiento continuó durante 2 horas adicionales. La mayoría del componente orgánico se evaporó y la porción restante se lavó con éter (20 ml). La capa acuosa se enfrió con baño de hielo-agua, se acidificó con HCl 1N hasta un pH de 2-3, se extrajo con EtOAc (50 ml, 4x), se secó con Na_2SO_4 y se concentró, proporcionando un aceite incoloro, que se convirtió en un sólido blanco tras la exposición a alto vacío (3.43g). El sólido se disolvió en una cantidad mínima de EtOAc con la ayuda de una pistola de calentamiento que lo llevó a un estado de reflujo. Después de enfriar hasta la temperatura ambiente se añadieron 5 gotas de hexano y se dejó reposar a temperatura ambiente durante la noche,

proporcionando el ácido GW9c en forma de agujas blancas, que se filtró y lavó con hexano, se secó al vacío (2.02g). RMN de ^{1}H ($CDCl_3$, δ = 7.24 ppm, 400 MHz) 4.40 (app dd, *J*=8.3, 2.8, 1H), 3.30 (m ancho, 1H), 2.50 (m ancho, 1H), 2.01-1.93 (m, 1H), 1.68-1.59 (m, 1H), 1.52 (s, 9H), 1.29 (d, *J*=6.0 , 3H), 1.07 (d, *J*=6.8 , 3H).

Ejemplo GW9, Etapa d



El compuesto GW9d (sal en TFA; espuma amarillo claro) se preparó a partir del ácido GW9c de acuerdo con el procedimiento descrito para la preparación de precursores GW3g del ácido GW3c con la excepción de que se empleó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico para la etapa final. RMN de ^{1}H (MeOD, δ = 3.30 ppm, 400 MHz): 7.97-7.96 (m, 2H), 7.88-7.82 (m, 8H), 5.70 (d ancho, *J* = 6.7, 0.6H), 5.29 (dd, *J* = 10.3, 1.2H), 5.19-5.14 (m, 0.2H), ~4.90 (solapado con señal HOD, 1H), 4.38 (m, 1H), 4.12-4.06 (m, 2H), 3.71/3.67/3.64 ('s' solapante, 6H), 2.73-2.68 (m, 0.6H), 2.53-2.45 (m, 1.4H), 2.35-2.18 (m, 2.5H), 2.07-1.82 (m, 3.5H), 1.53 (d, *J* = 6.8, 3.6H), 1.40 (d, *J* = 7.1, 0.5H), 1.30 (d, *J* = 7.1, 1.9H), 1.17-0.83 (colección de 'd' solapante,

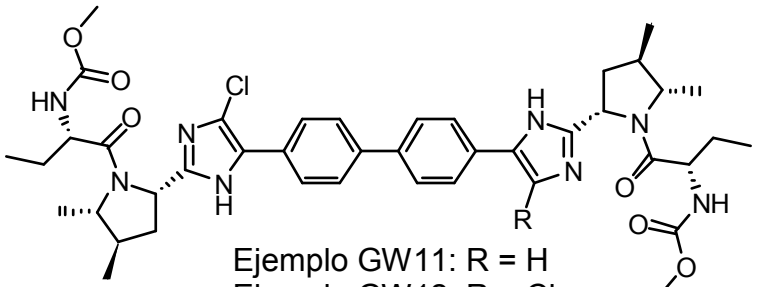
18H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TR = 2.07 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{59}N_8O_6$: 795.46; encontrado 795.44.

Ejemplos GW9 y GW10

A una solución GW9d (sal en TFA; 310 mg, 0.328 mmol) en DMF (6 ml) se añadió NCS (62.5 mg, 0.468 mmol) y la mezcla se calentó a 50°C durante 9 horas. La mayor parte del componente volátil se eliminó *a vacío* y el residuo se disolvió en MeOH y se sometió a purificación HPLC de fase inversa (MeOH/agua/TFA; columna: Phenomenex Luna, 30 X 100 mm S10 Axia) separando los productos mono y di-cloro. El producto monoclorado se purificó adicionalmente con una diferente condición de HPLC de fase inversa (ACN/TFA/Agua, Water-Sunfire 30X100 mm S5). El Ejemplo GW9 (espuma amarillo claro; 36 mg) y el Ejemplo GW10 (espuma amarillo claro; 60 mg) se recuperaron en forma de sales en TFA. Ejemplo GW9: RMN de ^1H (DMSO, δ = 2.50 ppm, 400 MHz): 12.71-12.64 (br m, 1H), 8.10 (s ancho, 1H), 7.95-7.83 (m, 8H), 7.64-7.58 (m, 1.4H), 7.51 (d, *J*=8.6, 0.6H), 5.56 (m, 0.22H), 5.33 (m, 0.33H), 5.16 (m, 0.78H), 5.04 (m, 0.67H), 4.27-4.11 (m, 2H), 3.93-3.86 ('m' solapado con la señal H_2O, 2H), 3.56-3.53 (m, 6H), 2.62-1.64 (colección de 'm', 8H), 1.50-0.75 (colección de 'd', 24H). CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TR = 2.66 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{58}ClN_8O_6$: 829.42; encontrado 829.44.

Ejemplo GW10: RMN de ^{1}H (DMSO, δ = 2.50 ppm, 400 MHz): 12.7 (m ancho, 2H), 8.00-7.80 (m, 8H), 7.63 (m, 0.76H), 7.51 (d, *J*=8.6, 1.09H), 7.08 (m, 0.09H), 6.57 (m, 0.05H), 5.33 (d, *J*=6.3, 0.74 H), 5.05 (app t, 1.26H), 4.25-4.12 (m, 2H), 3.90-3.85 ('m' solapado con señal de H_2O, 2H), 3.58-3.49 (m, 6H), 2.59-2.55 (m, 0.5H), 2.33-2.13 (m, 2.7H), 1.98-1.88 (m, 4.05H), 1.71-1.63 (m, 0.75H), 1.43 (d, *J*=6.6, 3.7H), 1.18 (d, *J*=6.3, 2.05H), 1.05-0.76 (colección de 'd', 18.25H), CL (Cond. 2a y 2b): índice de homogeneidad > 95%. EM/CL (Cond. Ia): TR = 3.29 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{57}Cl_2N_8O_6$: 863.38; encontrado 863.38.

Ejemplos GW11 y GW12

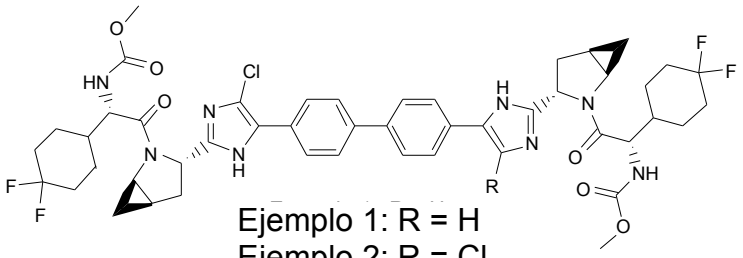


Ejemplo GW11: R = H
Ejemplo GW12: R = Cl

El Ejemplo GW11 y el Ejemplo GW12 se prepararon de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW9 y el Ejemplo GW10 con la excepción de que se usó ácido (S)-2-(metoxicarbonilamino)butanoico en lugar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico. Ejemplo GW11 (sal en TFA): EM/CL (Cond. Ia): TR = 2.57 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{54}ClN_8O_6$: 801.39; encontrado 801.38. Ejemplo GW12 (sal en TFA): EM/CL (Cond. Ia): TR = 3.24 min.

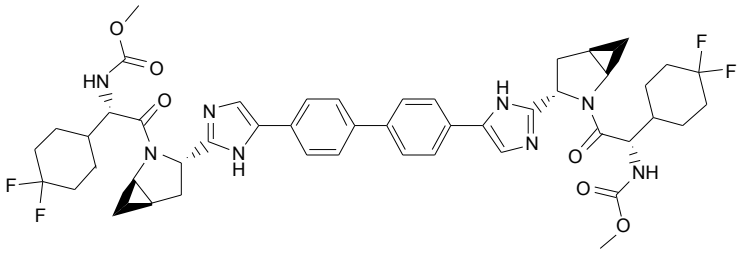
CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{53}Cl_2N_8O_6$: 835.35; encontrado 835.31.

Ejemplos OL1 y OL2



Ejemplo 1: R = H
Ejemplo 2: R = Cl

Ejemplo OL1, Etapa a



Los compuestos pirrolidina 1e/4HCl (455 mg, 0.766 mmol), ácido (S)-2-(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético (385 mg, 1.532 mmol), HATU (612 mg, 1.609 mmol) y DIEA (0.803 ml, 4.60 mmol) se combinaron en DMF (30 ml) y la solución amarillo resultante se agitó a temperatura ambiente durante 3 horas. El disolvente se eliminó a presión reducida y el residuo se redisolvió en metanol y se purificó HPLC preparatoria.(Disolvente A: 10% de acetonitrilo/90% de agua/NH_4Ac 10 mM ; Disolvente B: 90% de acetonitrilo/ 10% de agua/ NH_4OAc 10 mM ; Columna: Sunfire Prep MS C18 de 30 x 150mm S10; Longitud de onda: 220 nM; Caudal: 40 ml/min; gradiente: 10% de B a 75% de B durante 30 min con un tiempo de conservación de 30 minutos). Se

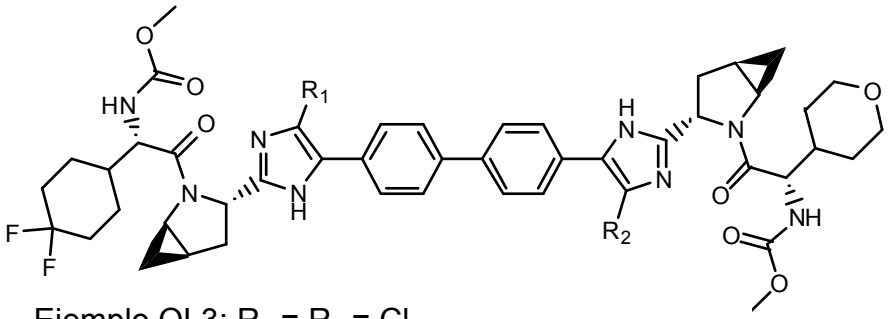
recuperó un sólido blancuzco correspondiente al producto OL1a (0.37 g, 0.396 mmol). RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 11.67 - 12.26 (2 H, m), 7.80 (4 H, d, *J*=7.93 Hz), 7.67 - 7.76 (1 H, m), 7.65 (4 H, d, *J*=8.24 Hz), 7.54 (2 H, s), 7.23 - 7.35 (2 H, m), 5.07 (2 H, dd, *J*=8.24, 3.66 Hz), 4.54 (2 H, t, *J*=7.93 Hz), 3.62 (2 H, d, *J*=4.27 Hz), 3.55 (6 H, s), 2.36 (2 H, t, *J*=10.99 Hz), 2.20 - 2.30 (2 H, m), 2.01 (4 H, s ancho,), 1.57 - 1.85 (9 H, m), 1.19 - 1.53 (6 H, m), 0.92 - 1.08 (2 H, m), 0.71 (2 H, br, s,). CL (Cond. OL3): T_r = 0.79 min. CL/EM: Anal. Calculado para $[M+H]^+$ $C_{48}H_{55}F_4N_8O_6$: 915.42; encontrado: 915.8. Evaluación de la pureza mediante HPLC (Cond. OL4a): T_a= 23.12 min; índice de homogeneidad = 98.4%.

Ejemplos OL1 y OL2

A una solución de la amida OL1a (39 mg, 0.043 mmol) en DMF (2 ml) se añadió NCS (6.83 mg, 0.051 mmol) y la mezcla resultante se calentó hasta 50°c durante 5 horas. Después, la mezcla de reacción se purificó mediante HPLC preparatoria. Disolvente A: MeOH al 10% /agua al 90% / TFA al 0.1% ; Disolvente B: MeOH al 90% /agua al 10% / TFA al 0.1% ; Columna: Sunfire Prep MS C18 de 30 x 100 mm de 5u; Longitud de onda: 220 nM; Caudal: 40 ml/min; gradiente: 0% de B a 75% de B durante 30 min con un tiempo de conservación de 2 minutos. Tras la

concentración de las fracciones, se aislaron las sales en TFA del Ejemplo OL1 (15 mg) y el Ejemplo OL2 (16 mg). Ejemplo OL1: RMN DE ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 8.11 (1 H, s), 7.74 - 8.00 (8 H, m), 7.40 (1 H, d, *J*=8.55 Hz), 7.28 (1 H, d, *J*=8.24 Hz), 4.91 - 5.05 (2 H, m), 4.48 - 4.59 (2 H, m), 3.74 - 3.87 (2 H, m), 3.62 - 3.71 (1 H, m), 3.55 (3 H, s), 3.54 (3 H, s), 2.19 - 2.43 (6 H, m), 1.66 - 2.07 (19 H, m), 1.56 (1 H, d, *J*=10.38 Hz), 1.26 - 1.48 (5 H, m), 0.89 - 1.02 (2 H, m), 0.81 (1 H, s), 0.70 (1 H, s ancho). CL (Cond. OL3): T_r = 0.87 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{54}ClF_4N_8O_6$: 949.38; encontrado: 949.6. Evaluación de la pureza mediante HPLC (Cond. OL4a): T_a= 9.16 min; índice de homogeneidad = 94.7 %. Ejemplo OL2: RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 7.86 (4 H, d, *J*=8.55 Hz), 7.79 (4 H, d, *J*=8.24 Hz), 7.29 (2 H, d, *J*=8.55 Hz), 4.95 (2 H, dd, *J*=8.55, 4.88 Hz), 4.52 (2 H, t, *J*=7.63 Hz), 3.67 (2 H, t, *J*=4.58 Hz), 3.54 (6 H, s), 2.21 - 2.40 (4 H, m), 2.01 (4 H, s ancho), 1.67 - 1.95 (13 H, m), 1.27 - 1.46 (4 H, m), 0.94 - 1.02 (2 H, m), 0.70 (2 H, d). CL (Cond. OL3): T_r = 1.01 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{53}Cl_2F_4N_8O_6$: 983.34; encontrado: 983.7. Evaluación de la pureza mediante HPLC (Cond. OL4a): T_a= 12.25 min; índice de homogeneidad = 94.7 %.

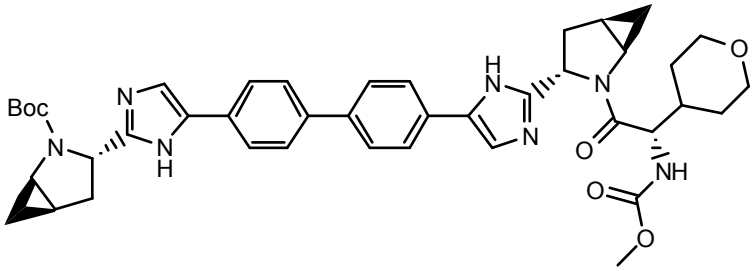
Ejemplos OL3 a OL5



Ejemplo OL3: $R_1 = R_2 = Cl$
Ejemplo OL4: $R_1/R_2 = Cl/H$
Ejemplo OL5: $R_1/R_2 = Cl/H$

No se determinó la regioquímica

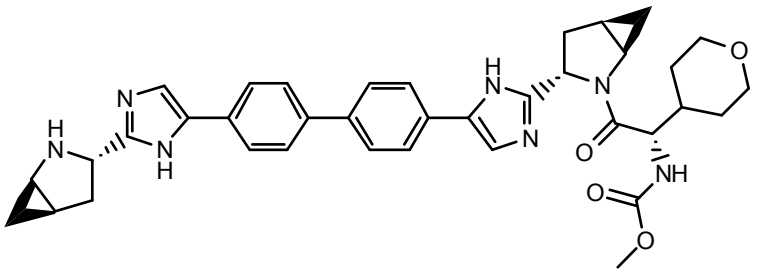
Ejemplo OL3, Etapa a



Los compuestos pirrolidina V9a (207 mg, 0.377 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (82 mg, 0.377 mmol), HATU (178 mg, 0.415 mmol) y DIEA (0.132 ml, 0.755 mmol) se combinaron en DMF (5 ml) y la solución amarilla resultante se agitó a temperatura ambiente durante 3 h. La mezcla se purificó mediante HPLC preparativa. Disolvente A: MeOH al 10% /agua al 90% / TFA al 0.1% ; Disolvente B: MeOH al 90% /agua al 10% / TFA al 0.1% ; Columna: Sunfire Prep MS C18 de 30 x 100 mm de 5u; Longitud de onda: 220 nM; Caudal: 40 ml/min; Gradiente: 20% de B a 80% de B durante 30 min con un tiempo de conservación de 2 minutos. Se recuperó un sólido blanco correspondiente a

la sal en TFA de carbamato OL3a (0.9 g) [Nota: los carbamatos O L3a y V9b son los mismos aparte de su estado]. RMN de ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 8.18 (1 H, s ancho), 8.12 (1 H, s), 7.80 - 8.00 (8 H, m), 7.34 (1 H, d, *J*=8.55 Hz), 5.01 (1 H, t, *J*=8.09 Hz), 4.79 - 4.90 (1 H, m), 4.49 (1 H, t, *J*=7.48 Hz), 3.74 - 3.87 (3 H, m), 3.55 (4 H, s), 3.18 - 3.32 (2 H, m), 2.52 - 2.59 (2 H, m), 2.37 (2 H, ddd, *J*=19.99, 13.43, 6.26 Hz), 2.07 (1 H, s ancho), 1.92 (1 H, dt, *J*=13.20, 6.68 Hz), 1.73 (1 H, ddd, *J*=13.20, 6.49, 6.26 Hz), 1.06 - 1.52 (17 H, m), 0.80 (2 H, s ancho), 0.74 (1 H, br, s,). CL (Cond. OL1): T_r = 1.98 min. CL/EM: Anal. Calc. para $[M+H]^+$ $]^+$ $C_{42}H_{50}N_7O_6$: 748.38; encontrado: 748.52.

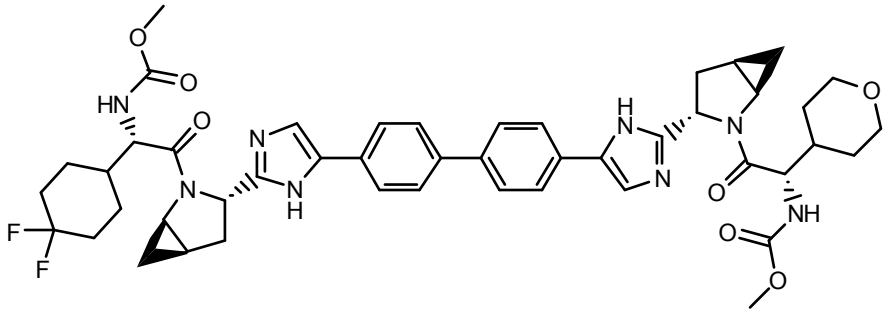
Ejemplo OL3, Etapa b



El carbamato OL3a (0.19 g, 0.195 mmol) se disolvió en CH_2Cl_2 (15 ml) y se cargó con HCl 4N en dioxanos (3 ml, 12.00 mmol). La suspensión resultante se agitó a temperatura ambiente durante 2 h y después se eliminaron los volátiles a presión reducida. Se recuperó un sólido amarillento correspondiente a la sal en TFA (3X) de pirrolidina OL3b (0.12 g) y se usó sin purificación adicional. RMN de ^{1}H (500 MHz, *DMSO-d_6*) δ ppm 8.14 (1 H, s), 7.83 - 8.01 (10 H, m),

7.34 (1 H, d, *J*=8.55 Hz), 5.06 (1 H, t, *J*=7.93 Hz), 4.73 (1 H, t, *J*=8.24 Hz), 4.50 (1 H, t, *J*=7.48 Hz), 3.78 - 3.87 (3 H, m), 3.64 - 3.74 (2 H, m), 3.56 (3 H, s), 3.44 - 3.51 (1 H, m), 3.39 - 3.44 (1 H, m), 3.20 - 3.35 (2 H, m), 2.55 - 2.64 (2 H, m), 2.34 - 2.43 (1 H, m), 2.06 - 2.16 (1 H, m), 1.87 - 1.97 (2 H, m), 1.27 - 1.51 (4 H, m), 1.12 (1 H, d, *J*=4.58 Hz), 0.90 - 0.98 (1 H, m), 0.82 - 0.89 (1 H, m), 0.78 (1 H, s ancho). CL (Cond. OL2): T_r = 2.51 min. CL/EM: Anal. Calc. para $[M+H]^+$]$^+$ $C_{37}H_{42}N_7O_4$: 648.33; encontrado: 648.4.

Ejemplo OL3, Etapa c



Los compuestos ácido (S)-2-(4,4-difluorociclohexil)-2-(metoxicarbonilamino)acético (87 mg, 0.345 mmol), la sal en TFA (3X) de la pirrolidina OL3b (261 mg, 0.345 mmol), HATU (144 mg, 0.379 mmol) y DIEA (0.301 ml, 1.724 mmol) se combinaron en DMF (10 ml) y la solución parduzca resultante se agitó a temperatura ambiente durante 2 horas. La muestra se purificó directamente mediante HPLC preparatoria. Disolvente A: MeOH al 10% /agua al 90% / TFA al 0.1% ; Disolvente B: MeOH al 90% /agua al 10% / TFA al 0.1% ; Columna: Sunfire Prep MS C18 de 30 x 100 mm de 5u;

Longitud de onda: 220 nM; Caudal: 40 mil/min; Gradiente: 30% de B a 70% de B durante 30 min con un tiempo de conservación de 2 minutos. Se recuperó un sólido blanco correspondiente a la sal en TFA (2x) de la amida OL3c (132 mg, 0.117 mmol, rendimiento del 33.8%). RMN de ^{1}H (500 MHz, *DMSO-d_6*) δ ppm 11.68 - 12.18 (2 H, m), 7.78 (3 H, t, *J*=8.39 Hz), 7.73 (1 H, d, *J*=9.46 Hz), 7.66 (4 H, d, *J*=8.55 Hz), 7.54 (2 H, dd, *J*=4.12, 1.68 Hz), 7.28 (2 H, dd, *J*=19.68, 8.39 Hz), 5.08 (2 H, ddd, *J*=8.39, 4.12, 3.97 Hz), 4.46 - 4.58 (2 H, m), 3.82 - 3.94 (2 H, m), 3.61 - 3.67 (2 H, m), 3.54 (6 H, d, *J*=1.53 Hz), 3.24 (2 H, t, *J*=11.29 Hz), 2.33 - 2.41 (2 H, m), 2.21 - 2.31 (2 H, m), 1.91 - 2.08 (4 H, m), 1.75 - 1.89 (6 H, m), 1.58 (1 H, d, *J*=13.43 Hz), 1.40 - 1.52 (2 H, m), 1.26 - 1.40 (3 H, m), 0.97 - 1.07 (2 H, m), 0.67 - 0.79 (2 H, m). CL (Cond. OL1): T_r = 1.94 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{47}H_{55}N_8O_7$: 881.42; encontrado: 881.58.

Ejemplos OL3 a OL5

A una solución de la sal en TFA del ejemplo OL3c (115 mg, 0.131 mmol) en DMF (3 ml) se añadió NCS (22.66 mg, 0.170 mmol) y la mezcla resultante se calentó hasta 50°c durante 5 horas. La mezcla de reacción se purificó mediante HPLC preparatoria. Disolvente A: MeCN al 0.5%/ agua al 95%/ NH_4Ac 10 mM; Disolvente B: MeCN al 95%/ agua al 5%/ NH_4Ac 10 mM ; Columna: Sunfire Prep MS C18 de 30 x 100 mm S10; Longitud de onda: 220 nM; Caudal: 35 ml/min; gradiente: 10%

de B a 100% de B durante 30 min con un tiempo de conservación de 2 minutos. Se aislaron dos fracciones, en las que el primer eluido correspondió a una mezcla de análogos monoclorados (Ejemplos OL4 y OL5) y el segundo correspondió a análogo bis-clorado (Ejemplo OL3). Después de la concentración de las dos fracciones correspondientes, la mezcla se redisolvió en metanol y los regioisómeros monoclorados se separaron mediante HPLC preparatoria. Disolvente A: Acetonitrilo al 10% / H_2O al 90% + TFA al 0.1%; Disolvente B: acetonitrilo al 90% /agua al 10% / TFA al 0.1% ; Columna: = Phenomenex-Luna 21 X 100mm S10; Longitud de onda: 220 nM; Caudal: 25 ml/min; gradiente: 10% de B a 50% de B durante 60 min con un tiempo de conservación de 2 minutos. Se aislaron dos fracciones, correspondientes al Ejemplo OL4 y al Ejemplo OL5) como TFA y no regioquímica relativa no se determinó.

El Ejemplo OL3 (36 mg) se recuperó en forma de un sólido blanco. RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 12.55 (2 H, d, *J*=1.22 Hz), 7.87 (4 H, d, *J*=8.24 Hz), 7.78 (4 H, d, *J*=7.02 Hz), 7.27 (2 H, dd, *J*=18.62, 8.55 Hz), 5.76 (1 H, s), 4.91 - 5.01 (2 H, m), 4.45 - 4.58 (2 H, m), 3.85 (2 H, d, *J*=9.77 Hz), 3.64 - 3.71 (2 H, m), 3.54 (6 H, s), 3.20 - 3.31 (2 H, m), 2.21 - 2.35 (4 H, m), 2.02 (3 H, d, *J*=3.97 Hz), 1.59 - 1.93 (9 H, m), 1.21 - 1.55 (7 H, m), 0.93 - 1.02 (2 H, m), 0.71 (2 H, m). CL (Cond. OL3): T_r = 0.95 min. CL/EM:

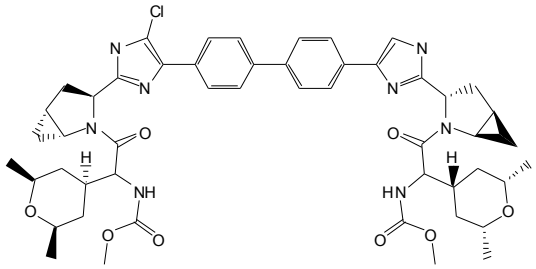
Anal. Calc. para $[M+H]^+$ $C_{47}H_{53}Cl_2F_2N_8O_7$: 949.34; encontrado: 949.8. Evaluación de la pureza mediante HPLC (Cond. OL4b): T_a= 11.10 min; índice de homogeneidad = 100 %.

El Ejemplo OL4 (10 mg) se recuperó en forma de un sólido blanco. RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 14.62 (1 H, s ancho), 12.59 (1 H, s ancho), 8.12 (1 H, s ancho), 7.87 (8 H, dd, *J*=19.38, 8.09 Hz), 7.80 (2 H, d, *J*=7.63 Hz), 7.40 (1 H, d, *J*=8.85 Hz), 7.26 (1 H, d, *J*=8.24 Hz), 5.00 (1 H, t, *J*=7.93 Hz), 4.95 (1 H, dd, *J*=8.39, 5.04 Hz), 4.54 (1 H, t, *J*=7.48 Hz), 4.49 (1 H, t, *J*=7.93 Hz), 3.86 (3 H, dd, *J*=11.44, 2.59 Hz), 3.79 (1 H, br, s,), 3.65 - 3.72 (2 H, m), 3.55 (6 H, d, *J*=5.19 Hz), 3.19 - 3.28 (2 H, m), 2.20 - 2.43 (4 H, m), 1.89 - 2.07 (5 H, m), 1.30 - 1.89 (10 H, m), 0.92 - 1.03 (2 H, m), 0.80 (1 H, s ancho), 0.72 (1 H, s ancho) LC (Cond. OL3): T_r = 0.85 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{47}H_{54}ClF_2N_8O_7$: 915.38; encontrado: 915.9. Evaluación de la pureza mediante HPLC (Cond. OL4a): T_a= 9.03 min; índice de homogeneidad = 100 %.

El Ejemplo OL5 (12 mg, rendimiento del 7.96%) se recuperó en forma de un sólido blanco. RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 14.62 (1 H, s ancho), 12.59 (1 H, s ancho), 8.09 (1 H, s ancho), 7.87 - 7.98 (4 H, m), 7.84 (2 H, d, *J*=8.24 Hz), 7.80 (2 H, d, *J*=8.24 Hz), 7.35 (1 H, d, *J*=8.24 Hz), 7.29 (1 H, d, *J*=8.55 Hz), 4.91 - 5.03 (2 H, m), 4.51 (2 H, ddd, *J*=15.64, 7.71, 7.48 Hz), 3.78 - 3.90 (4 H, m), 3.64 -

3.71 (1 H, m), 3.54 (6 H, s), 3.16 - 3.31 (2 H, m), 2.19 - 2.44 (3 H, m), 2.02 (3 H, s ancho), 1.64 - 1.95 (7 H, m), 1.27 - 1.54 (6 H, m), 0.96 (2 H, dd, *J*=12.21, 7.32 Hz), 0.81 (1 H, s ancho), 0.70 (1 H, s ancho). CL (Cond. OL3): T_r = 0.86 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{47}H_{54}ClF_2N_8O_7$: 915.38; encontrado: 915.9. Evaluación de la pureza mediante HPLC (Cond. OL4a): T_a= 8.11 min; índice de homogeneidad = 100 %.

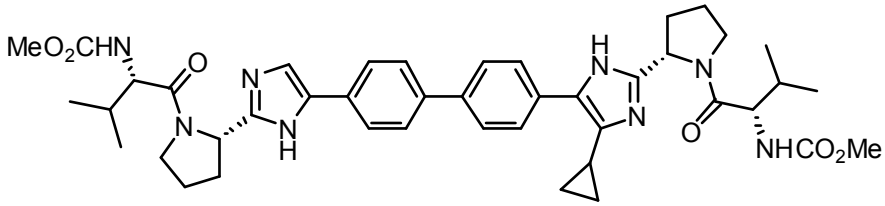
Ejemplo OL6



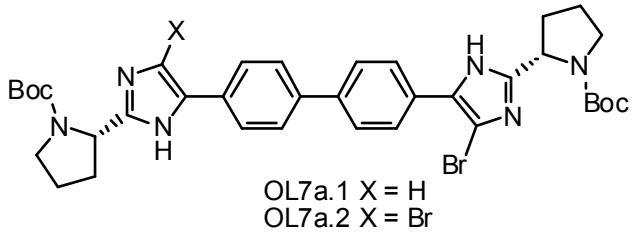
Se puede preparar el *Ejemplo OL6* (sal de TFA) partiendo de pirrolidina V1b/4HCl y *Cap 179 (Enantiómero-1)* según el procedimiento descrito para la síntesis de *Ejemplo V1*. RMN de ^{1}H (400 MHz, *DMSO-d*$_6$) δ ppm 8.11 (1 H, s ancho), 7.74 - 8.01 (8 H, m), 7.22 - 7.35 (1 H, m), 7.14 (1 H, d, *J*=7.53 Hz), 4.87 - 5.15 (2 H, m), 4.47 (2 H, d, *J*=7.03 Hz), 3.80 (1 H, s ancho), 3.65 (1 H, s ancho), 3.55 (6 H, s ancho), 3.36 (4 H, s ancho), 2.20 - 2.37 (3 H, m), 2.13 (1 H, s ancho), 1.90 - 2.05 (2 H, m), 1.85 (1 H, s ancho), 1.63 - 1.80 (1 H, m), 1.38 - 1.61 (2 H, m), 0.62 - 1.14 (25 H, m). CL (Cond. 2a y 2b): índice de homogeneidad >95%. CL (Cond. OL4c): T_r = 0.85 min. CL/EM: anal. calcd. para $[M+H]^+$

$C_{50}H_{62}ClN_8O_8$: 937.44; encontrado: 937.5.

Ejemplo OL7

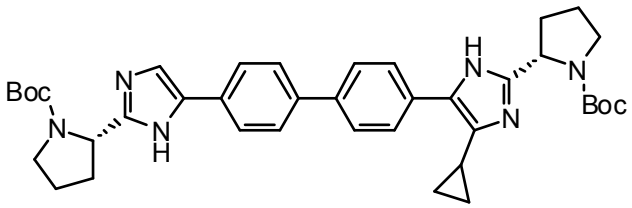


Ejemplo OL7, Etapa a



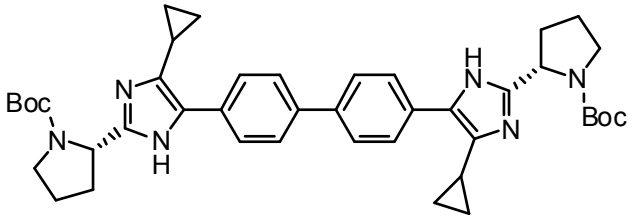
A una solución de 2.2'-(5.5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-terc-butilo (500 mg, 0.800 mmol) en AcOH (30 ml) se añadió bromo (0.041 ml, 0.800 mmol) en AcOH (0.8 ml) gota a gota durante 10 min. La mezcla de reacción resultante se agitó a temperatura ambiente durante toda una noche, se neutralizó con $NaHCO_3$ saturado, se extrajo después con CH_2Cl_2. Las fases orgánicas se secaron con $MgSO_4$ y se concentraron a vacío. El material resultante se purificó por cromatografía ultrarrápida (gel de sílice; EtOAc/Hexano 1:1 después EtOAc/Hexano 2:1) proporcionando bromuro OL7a.1 (200 mg) y dibromuro OL7a.2 (140 mg) como sólidos blancos (nota: el dibromuro eluyó primero de la columna).

Ejemplo OL7, Etapa b.1



Una mezcla de ácido ciclopropilborónico (13.49 mg, 0.157 mmol), fosfato de potasio tribásico (90 mg, 0.423 mmol) en agua (0.03 ml) se agitó a temperatura ambiente durante 15 minutos. Se añadieron después bromuro OL7a.1 (85 mg, 0.121 mmol), acetato de Pd(II) (2.71 mg, 0.012 mmol), triciclohexilfosfina (6.8 mg, 0.024 mmol) y tolueno (1 ml) y la mezcla de reacción se agitó a 110°C durante toda una noche. El componente volátil se retiró al vacío y el residuo se purificó por HPLC preparativa usando la siguiente condición. Columna: WATERS-Sunfire OBD 19 X 100 mm S5; Disolvente A = ACN al 10%-H_2O al 90%-TFA al 0.1%; Disolvente B = ACN al 90%-H_2O al 10%-TFA al 0.1%; % inicial de B = 10; % final de B = 75; velocidad de flujo = 20 ml/min; tiempo de gradiente = 20 min. La sal de TFA del producto acoplado OL7b.1 se recuperó en forma de un sólido amarillo claro (79 mg).

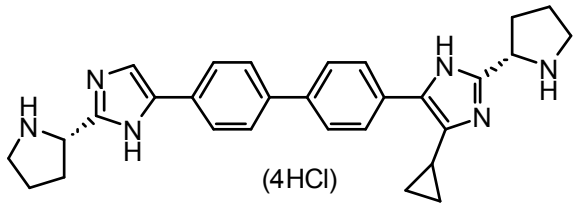
Ejemplo OL7, Etapa b.2



Una mezcla de dibromuro OL7a.2 (140 mg, 0.179

mmol), ácido ciclopropilborónico (40.0 mg, 0.465 mmol), acetate de Pd(II) (8.03 mg, 0.036 mmol), fosfato de potasio tribásico (266 mg, 1.252 mmol), triciclohexilfosfina (20.07 mg, 0.072 mmol) en tolueno (1.5 ml) y agua (0.05 ml) se calentó con un microondas a 110°C durante 1.5 horas. CLEM mostró que no hay ninguna reacción. La mezcla se filtró y el filtrado se concentró al vacío y el producto en bruto resultante se purificó por HPLC prep.: columna = WATERS-Sunfire OBD 19 X 100 mm S5; disolvente A = ACN al 10%-H_2O al 90%-TFA al 0.1%; disolvente B = ACN al 90%-H_2O al 10%-TFA al 0.1%; % inicial de B = 10. % final de B = 70; velocidad de flujo = 20 ml/min; tiempo de gradiente = 20 min. La sal de TFA del producto acoplado OL7b.2 se obtuvo en forma de un sólido amarillo.

Ejemplo OL7, Etapa c



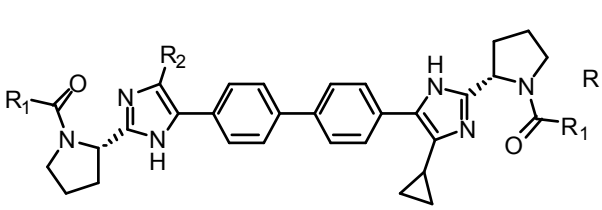
A una solución de carbamato OL7b preparada anteriormente (79 mg) en CH_2Cl_2 (2 ml) se añadió HCl (2 ml, 8.00 mmol) (4 N en dioxano) y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos. El componente volátil se retiró a vacío proporcionando la sal de HCl de OL7c (69 mg), que se usó en la siguiente etapa sin purificación adicional.

Ejemplo OL7

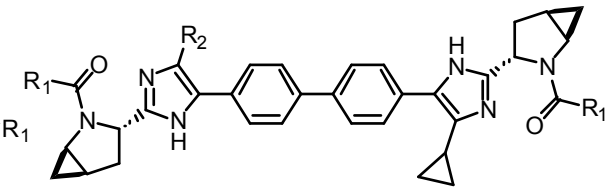
A una mezcla de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (20.09 mg, 0.115 mmol), pirrolidina OL7/4 HCl (35 mg, 0.057 mmol) en DMF (1 ml) se añadió DiPEA (0.06 ml, 0.34 mmol) y HATU (43.6 mg, 0.115 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora y después se añadió amoniaco (2 ml, 2 M en metanol) y la agitación se continuó durante 1 hora adicional. El componente volátil se retiró al vacío y el residuo se purificó por columna de HPLC preparativa: columna = WATERS Sunfire C18 19 X 100 mm 5u; Disolvente A = MeOH al 10%-H_2O al 90%-TFA al 0.1%; disolvente B = MeOH al 90%-H_2O al 10%-TFA al 0.1%; % inicial de B = 10; % final de B = 75; velocidad de flujo = 25 ml/min; tiempo de gradiente = 18 min. La sal de TFA del Ejemplo OL7 se obtuvo como un sólido blanquecino (24 mg). Tr = 1.68 min (Cond. OL5a). $(M+H)^+$ 779.47. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 8.12 (1 H, s ancho), 7.97 (4 H, dd, *J*=12.97, 8.39 Hz), 7.86 – 7.92 (2 H, m), 7.80 (2 H, d, *J*=8.24 Hz), 7.32 (2 H, t, *J*=8.70 Hz), 5.14 (1 H, t, *J*=7.02 Hz), 5.05 (1 H, t, *J*=7.48 Hz), 4.12 (2 H, t, *J*=6.71 Hz), 3.76 - 3.92 (4 H, m), 3.54 (6 H, s), 2.39 (2 H, d, *J*=6.10 Hz), 1.95 - 2.21 (9 H, m), 1.08 (2 H, d, *J*=8.24 Hz), 0.84 (7 H, t, *J*=7.17 Hz), 0.79 (6 H, d, *J*=6.41 Hz), 0.67 - 0.74 (1 H, m).

Ejemplos OL8 a OL14

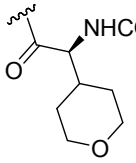
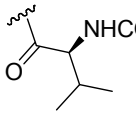
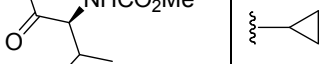
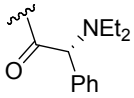
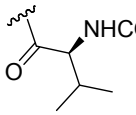
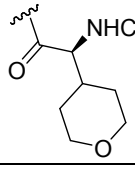
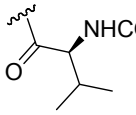
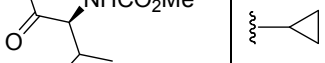
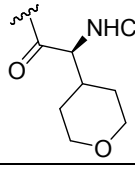
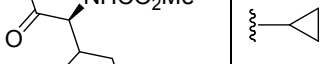
Se prepararon los Ejemplos OL8 – OL14 como sales de TFA empleando los precursores apropiados y el procedimiento descrito para la preparación del Ejemplo OL7.



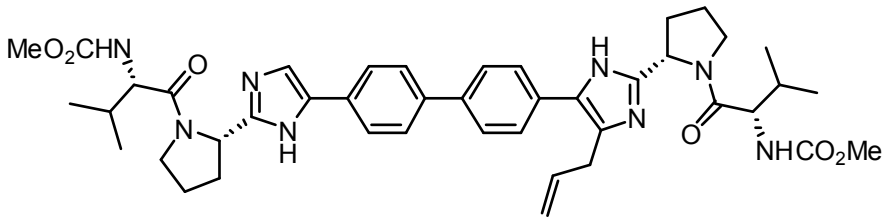
Ejemplo OL8-OL10



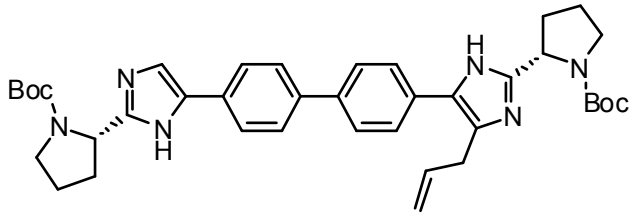
Ejemplo OL11-OL14

Ejemplo		R_2	Tr (Condición). CL/EM $(M+H)^+$ observada
OL8		H	Tr = 1.49 min (Cond. OL5a). $(M+H)^+$ 863.48
OL9			Tr = 1.77 min (Cond. OL5a). $(M+H)^+$ 819.55
OL10			Tr = 1.54 min (Cond. OL5a). $(M+H)^+$ 883.51
OL11		H	Tr = 1.74 min (Cond. OL5a). $(M+H)^+$ 803.41
OL12		H	Tr = 2.40 min (Cond. OL5b). $(M+H)^+$ 887.60
OL13			Tr = 1.87 min (Cond. OL5a). $(M+H)^+$ 843.39
OL14			Tr = 2.55 min (Cond. OL5b). $[(M+H)/2]^+$ = 464.36

Ejemplo OL15



Ejemplo OL15, Etapa a

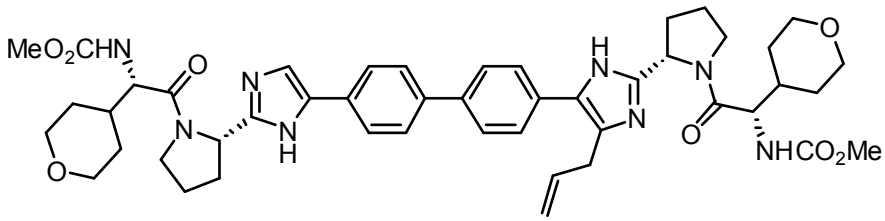


Una mezcla de bromuro OL7a.1 (200 mg, 0.284 mmol), CsF (0.021 ml, 0.568 mmol), $Pd(Ph_3P)_4$ (19.71 mg, 0.017 mmol) y 2-alil-4,4,5,5-tetrametil-1,3,2-dioxaborolano (0.107 ml, 0.568 mmol) en THF (3 ml) se calentó a 140°C en microondas durante 1 hora. El disolvente se retiró al vacío y el residuo se purificó por HPLC preparativa. Columna, Phenomenex Luna 10u (30 X 100 mm); disolvente A = CH_3CN al 5%-H_2O al 95%-NH_4OAc 10 mm; disolvente B = CH_3CN al 95%-H_2O al 5%-NH_4OAc 10 mm; % inicial de B = 30; % final de B = 100; velocidad de flujo = 25 ml/min; Tiempo de gradiente = 48 min. Se obtuvo el producto OL15a en forma de un sólido blanco (90 mg).

Ejemplo OL15

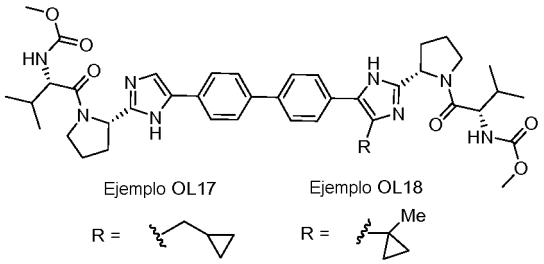
Se elaboró carbamato OL15a para la sal TFA de Ejemplo OL15 según el procedimiento descrito para la síntesis del Ejemplo OL7. Tr = 1.73 min (Cond. OL5a). $(M+H)^+$ 779.53.

Ejemplo OL16



Se preparó Ejemplo OL16 (sal de TFA) a partir de precursores apropiados según el procedimiento descrito para la síntesis del Ejemplo OL15. Tr = 1.73 min (Cond. OL5a). $(M+H)^+$ 863.11.

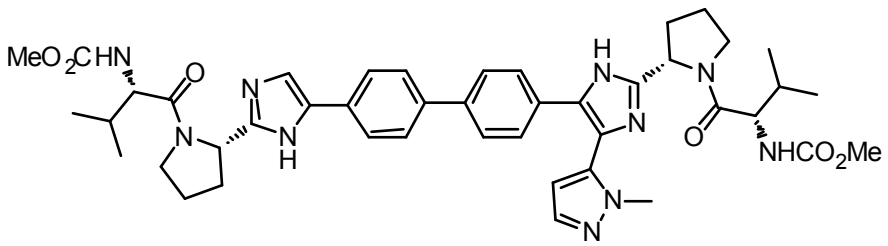
Ejemplos OL17 y OL18



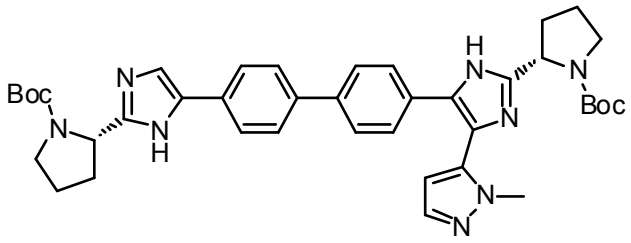
A una solución de OL15a (70 mg, 0.105 mmol), diyodometano (0.102 ml, 1.263 mmol) en tolueno (0.5 ml) a 0°C se añadió rápidamente dietilcinc (1.263 ml, 1.263 mmol) (1 M en heptano). La mezcla resultante se agitó a 0°C durante 1.5 horas después a temperature ambiente durante 4 horas. A la mezcla se añadió una solución de $NaHCO_3$ acuosa saturada y la mezcla se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron bajo $MgSO_4$ y se concentraron. El residuo se purificó por HPLC preparatoria: columna, Phenomenex Luna 10u (30 X 100 mm); disolvente A = CH_3CN al 5%-H_2O al 95%-NH_4OAc 10 mm; disolvente B = CH_3CN al 95%-H_2O al 5%-NH_4OAc 10 mm; % inicial de B = 30; % final de B = 100; velocidad de flujo =

25 ml/min. Tiempo de gradiente = 25 min. El material resultante (sólido blanco, 40 mg) se disolvió en CH_2Cl_2 (1 ml) y se trató con HCl (1 ml, 4.00 mmol) (4 N en dioxano). La mezcla se agitó a temperature ambiente durante 1 hora. El componente volátil se retiró a vacío proporcionando un producto (35 mg), que se acopló con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico de acuerdo con el procedimiento descrito para la síntesis del Ejemplo OL7. El residuo en bruto obtenido se purificó por HPLC preparativo: columna = WATERS Sunfire C18 19 X 100 mm 5u; disolvente A = MeOH al 10%-H_2O al 90%-TFA al 0.1%; disolvente B = MeOH al 90%-H_2O al 10%-TFA al 0.1%; % inicial de B = 20; % final de B = 85; caudal = 25 ml/min; tiempo de gradiente = 27 min. Se aislaron dos fracciones, donde el primero a eluir correspondió a la sal de TFA del Ejemplo OL18 (Tr = 1.74 min (Cond. OL5a). $(M+H)^+$ 793.54) y el segundo a eluir correspondió a la sal de TFA del Ejemplo OL17 (Tr = 1.77 min (Cond. OL5a). $(M+H)^+$ 793.53).

Ejemplo OL19

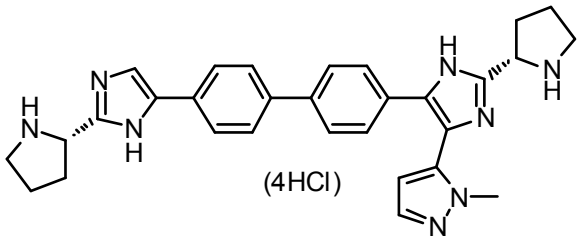


Ejemplo OL19, Etapa a



Una mezcla de 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (59.1 mg, 0.284 mmol), fosfato de potasio tribásico (121 mg, 0.568 mmol) en agua (0.2 mL) se agitó a temperatura ambiente durante 15 min. Se añadieron después bromuro OL7a.1 (100 mg, 0.142 mmol), $Pd(Ph_3P)_4$ (9.85 mg, 0.008 mmol y DMF (2 ml) y la mezcla de reacción se agitó durante 40 minutos a 130°C en radiación de microondas. El componente volátil se retiró a vacío y el residuo se purificó por HPLC preparativa usando la siguiente condición. Columna: Phenomenex Luna 10u (30 X 100 mm); disolvente A = ACN al 10%-H_2O al 90%-NH_4OAc 10 mm; disolvente B = ACN al 90%-H_2O al 10%-NH_4OAc 10 mm; % inicial de B = 10; % final de B = 80; caudal = 25 ml/min; tiempo de gradiente = 15 min. El producto acoplado OL19a se recuperó en forma de un sólido amarillo claro (120 mg).

Ejemplo OL19, Etapa b



A una solución de carbamato OL19a preparada

anteriormente (120 mg) en CH_2Cl_2 (1 ml) se añadió HCl (1 ml, 4.00 mmol) (4 N en dioxano), y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. El componente volátil se retiró a vacío proporcionando la sal de HCl de OL19b (87 mg), que se usó en la siguiente etapa sin purificación adicional.

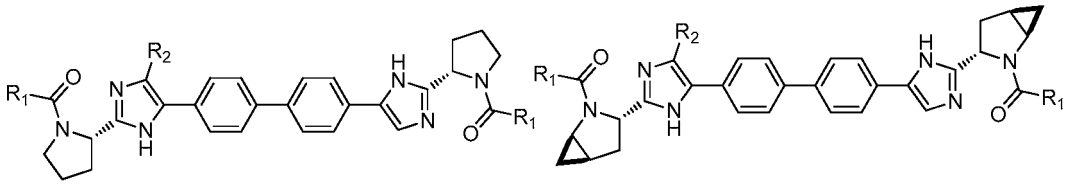
Ejemplo OL19

A una mezcla de ácido (S)-2-(metoxocarbonilamino)-3-metilbutanoico (15.30 mg, 0.087 mmol), pirrolidina OL19b/4 HCl (30 mg, 0.044 mmol) en DMF (1 mL) se añadió DiPEA (0.053 ml, 0.306 mmol) y HATU (33.2 mg, 0.087 mmol). La mezca de reacción se agitó a temperature ambiente durante 1 hora, el componente volátil se retiró al vacío y el residuo se purificó por HPLC preparativa: columna = WATERS Atlantis OBD 30 X 100 mm 5u; disolvente A = MeOH al 10%-H_2O al 90%-TFA al 0.1%; disolvente B = MeOH al 90%-H_2O al 10%-TFA al 0.1%; % inicial de B = 20; % final de B = 75; caudal = 25 ml/min; tiempo de gradiente = 25 min. La sal de TFA del Ejemplo OL19 se obtuvo como un sólido blanco (33 mg). Tr = 1.63 min (Cond. OL5a). $(M+H)^+$ 819.40. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 8.13 (1 H, s), 7.88 – 7.96 (2 H, m), 7.78 – 7.88 (4 H, m), 7.57 (1 H, s ancho), 7.43 – 7.51 (2 H, m), 7.33 (2 H, dd, *J*=8.39, 3.51 Hz), 6.42 (1 H, s ancho), 5.10 – 5.18 (2 H, m), 4.11 (2 H, td, *J*=7.93, 2.75 Hz), 3.78 - 3.91 (4 H, m), 3.59 - 3.66 (3 H, m), 3.54 (6 H, d, *J*=1.53 Hz), 2.35 - 2.45 (1 H, m), 2.30

(1 H, d, *J*=7.32 Hz), 2.13 - 2.22 (2 H, m), 1.93 - 2.13 (6 H, m), 0.89 (5 H, d, *J*=6.71 Hz), 0.83 (6 H, t, *J*=6.87 Hz), 0.78 (3 H, d, *J*=6.71 Hz).

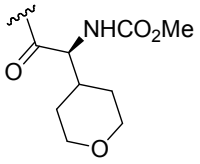
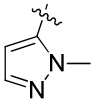
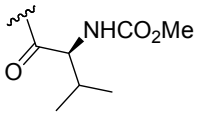
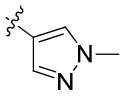
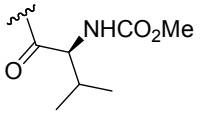
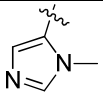
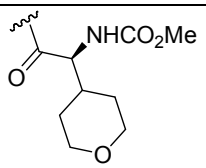
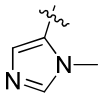
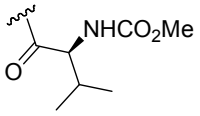
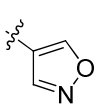
Ejemplos OL20 a OL25

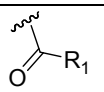
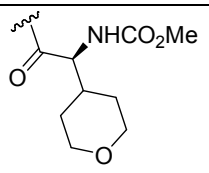
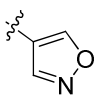
Los ejemplos OL20 a OL25 se prepararon como sales de TFA empleando los precursors apropiados y el procedimiento descrito por la preparación del Ejemplo OL19.



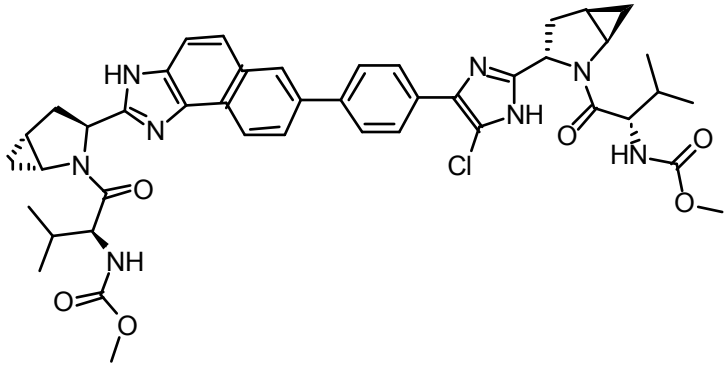
Ejemplo OL20-OL23

Ejemplo OL24-OL25

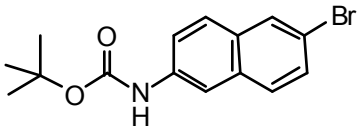
Ejemplo		R_2	Tr (Condición). CL/EM $(M+H)^+$ observada
OL20			Tr = 2.19 min (Cond. OL5b). $(M+H)^+$ 903.65
OL21			Tr = 1.56 min (Cond. OL5a). $(M+H)^+$ 819.39
OL22			Tr = 1.43 min (Cond. OL5a). $(M+H)^+$ 816.66
OL23			Tr = 1.27 min (Cond. OL5a). $(M+H)^+$ 903.61
OL24			Tr = 1.83 min (Cond. OL5a). $(M+H)^+$ 830.50

Ejemplo		R_2	Tr (Condición). CL/EM $(M+H)^+$ observada
OL25			Tr = 1.62 min (Cond. OL5a). $[(M+H)/2]^+$ 457.6

Ejemplo DSTL-1



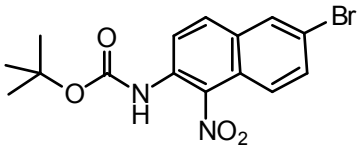
Ejemplo DSTL-1, Etapa a



A una solución de ácido 6-bromo-2-naftoico (16.5 g, 65.7 mmol), trietilamina (18.32 ml, 131 mmol) y alcohol terc-butílico (7.54 ml, 79 mmol) en tolueno (225 ml) se añadió difenilfosforilazida (17.09 ml, 79 mmol) y se agitó durante 4 horas a 1001C. Los volátiles se eliminaron mediante evaporación rotatoria y el residuo se suspendió en EtOAc (500 ml) y se lavó con agua y salmuera. Tras la concentración se formó un precipitado, que se aisló mediante filtración y se lavó con Et_2O/Hex a 1:1 ara dar el Ejemplo DSTL-1, etapa a (10.5 g). Se aisló una segunda cosecha de producto menos

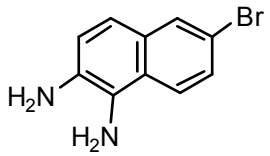
puro tras la concentración del licor madre (9.8 g); rendimiento combinado (93%). EM/CL (Cond. J4): TR = 3.44 min. CL/EM Anal. Calculado para $[M+Na]^+$ $C_{15}H_{16}BrNO_2$: 345.02; encontrado 345.03.

Ejemplo *DSTL-1, Etapa b*



El Ejemplo DSTL-1, etapa a (5 g, 15.52 mmol) se diluyó en ácido acético (50 ml) y, gota a gota, se añadió ácido nítrico ahumado (2.3 ml) durante 20 min. La reacción se agitó durante 2 horas y el producto, aislado mediante filtración, se repartió entre DCM y solución de $NaHCO_3$ saturado. La capa orgánica se concentró y se obtuvo el Ejemplo DSTL-1, etapa b, 5.7 g (cant.). EM/CL (Cond. J4): TR = 3.52 min. CL/EM Anal. Calculado para $[M+Na]^+$ $C_{15}H_{15}BrN_2O_4$: 390.02; encontrado 390.99.

Ejemplo *DSTL-1, Etapa c*

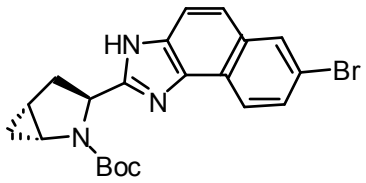


Sal HCl

A una solución del Ejemplo DSTL-1, etapa b (2 g, 5.47 mmol) en MeOH (100 ml) se añadió cloruro de estaño (II) dihidrato (3 g, 16.34 mmol) y la solución se agitó durante 18 horas a 70 °C. El disolvente se eliminó mediante evaporación rotatoria y el Ejemplo DSTL-1, etapa c,

(suposición teórica 1.25 g) se secó en alto vacío. EM/CL (Cond. J4): TR = 1.49 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{10}H_9BrN_2$: 237.00; encontrado 236.96.

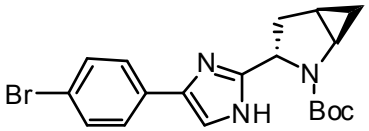
Ejemplo *DSTL-1, Etapa d*



A una solución del Ejemplo DSTL-1, etapa c (1.25 g, 5.48 mmol), el ejemplo 1, etapa b (1.246 g, 5.48 mmol) y base de Hunig (7.09 g, 54.8 mmol) en DMF (70 ml) se añadió HATU (2.085 g, 5.48 mmol) y la mezcla de reacción se agitó durante 6 horas antes de repartirse entre EtOAc (500 ml) y $NaHCO_3$ saturado (150 ml). Las sales de estaño que precipitaron se eliminaron mediante filtración en celite y la fase orgánica se concentró dando un residuo que se suspendió en AcOH (100 ml) y se calentó a 60 °C durante 18 horas. El disolvente se eliminó mediante evaporación rotatoria en alto vacío y el residuo se suspendió en CH_2Cl_2 y se lavó con solución de $NaHCO_3$ saturado. Después de concentrar, el producto en bruto se cargó (DCM) en un cartucho de gel de sílice Thompson (110 g) y se sometió a elución por gradiente; 15 - 100% de B durante 1 l dando el Ejemplo DSTL-1, etapa d (420 mg, 44 %). EM/CL (Cond. J4): TR = 2.51 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{21}H_{22}BrN_3O_2$: 430.10;

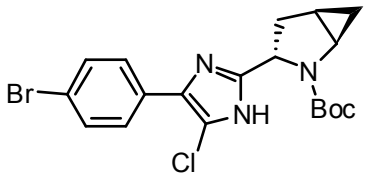
encontrado 430.06.

Ejemplo *DSTL-1, etapa d.1*



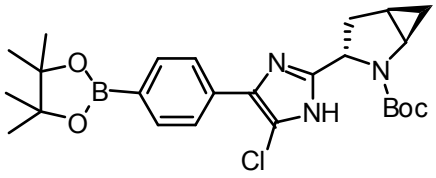
El Ejemplo DSTL-1, etapa d.1 se preparó a partir del Ejemplo 1, etapa b, de acuerdo con el procedimiento descrito para la síntesis de su análogo desmetano en la solicitud de patente WO2008/021927.

Ejemplo *DSTL-1, Etapa e*



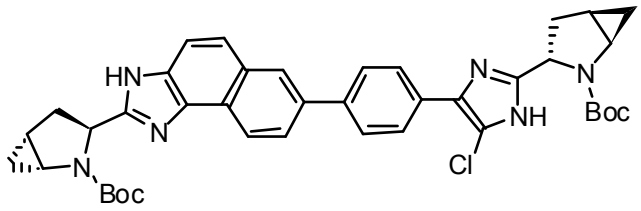
A una solución del Ejemplo DSTL-1, etapa d.1 (560 mg, 1.39 mmol) en DMF (15 ml) se añadió NCS (203 mg, 1.52 mmol). La mezcla de reacción se calentó a 50 °C durante 16 h. La solución se purgó con nitrógeno evaporando DMF y el residuo en bruto se cargó (DCM) en una columna Thompson de SiO_2 (80 g) y se realizó elución por gradiente (Biotage). Segmento 1: 10-100% de B en 1.5 l. Segmento 2: Conservación 100% B 300 ml. (A/B Hexanos/EtOAc). Se aisló el Ejemplo DSTL-1, etapa e (589.1 mg, rendimiento del 92 %). EM/CL (Cond.-D4): TR = 2.61 min. CL/EM Anal. Calculado para $[M+Na]^+$ $C_{19}H_{22}ClN_3O$: 462.04; encontrado 462.07.

Ejemplo *DSTL-1, Etapa f*



Se añadió tetrakis(trifenilfosfina) paladio (76 mg, 0.066 mmol) se añadió en una porción a una suspensión agitada del Ejemplo DSTL-1, etapa e (580 mg, 1.32 mmol), bis(pinacolato)diboro (671 mg, 2.64 mmol) y acetato potásico (324 mg, 3.30 mmol) en una solución de dioxano (12 ml) en un vaso a presión con tapa de rosca. La mezcla de reacción se evacuó y se lavó con argón (3x) y se introdujo en un baño de aceite precalentado (0°C) y se agitó durante 16 horas. Después de enfriar, la mezcla de reacción se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturado, salmuera y se secó sobre Na_2SO_4. El residuo bruto se cargó (DCM) en una columna Thompson de SiO_2 (80 g) y se efectuó elución por gradiente (Biotage). Segmento 1: 5-100% de B en 1.5 l. Segmento 2: Conservación 100% B 300 ml. (A/B CH_2Cl_2/EtOAc). Se aisló el Ejemplo DSTL-1, etapa f (714.7 mg, rendimiento del 95%) en forma de espuma amarilla. EM/CL (Cond.-D4): TR = 2.69 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{25}H_{34}BClN_3O_4$: 486.24; encontrado 486.26.

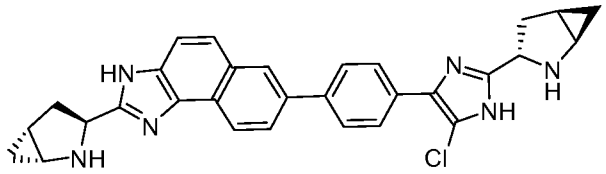
Ejemplo *DSTL-1, Etapa g*



Se añadió tetrakis(trifenilfosfina) paladio (27.0 mg, 0.023 mmol) se añadió en una porción a una suspensión

agitada del Ejemplo DSTL-1, etapa d (200 mg, 0.467 mmol), el Ejemplo DSTL-1, etapa f (250 mg, 0.514 mmol) y $NaHCO_3$ (196 mg, 2.335 mmol) en una solución desgasificada de DME (4 ml) y agua (1 ml) en argón en un vaso a presión con tapa de rosca. La solución se evacuó y se cargó con argón (3x) y se introdujo en un baño de aceite precalentado (80°C) y se agitó durante 14 horas. La mezcla se diluyó con EtOAc (10 ml), THF (2 ml) y MeOH (1 ml), se lavó con salmuera y se secó sobre Na_2SO_4. Después de concentrar para eliminar el disolvente, el residuo se cargó en una columna Thompson de SiO_2 (80 g) y se eluyó (Biotage) por gradiente. Segmento 1: 20-100% de B en 1.5 l. Segmento 2: Conservación 100% de B para 300 ml; A/B Hexanos/EtOAc. Se aisló el Ejemplo DSTL-1, etapa g (195.0 mg, 52.6%) en forma de un sólido marrón. EM/CL (Cond.-D4): TR = 2.40 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{44}ClN_6O_4$: 707.31; encontrado 707.43.

Ejemplo *DSTL-1, Etapa h*



sal HCl

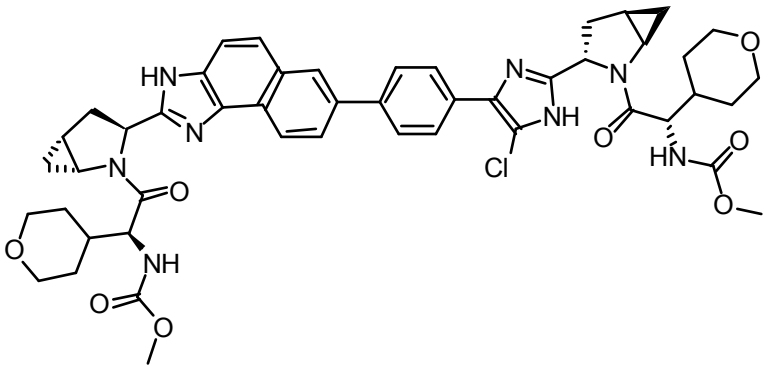
A una solución agitada del Ejemplo DSTL-1, etapa g (65 mg, 0.092 mmol) en MeOH (1 ml) se añadió HCl 4N frío (0°C). La mezcla se agitó a temperatura ambiente durante 3 horas, se concentró y se introdujo en alto vacío proporcionando el DSTL-1, etapa h, en forma de un sólido

naranja-marrón y en forma de una sal de tetra HCl. EM/CL (Cond.-D4): TR = 1.63 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{30}H_{28}ClN_6$: 507.21; encontrado 507.26.

Ejemplo *DSTL-1*

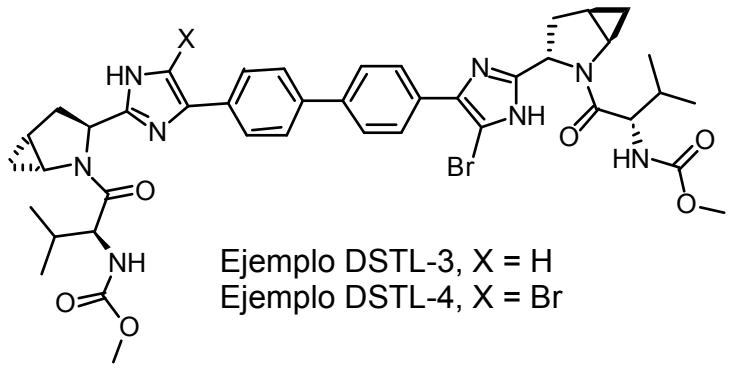
El Ejemplo DSTL-1 se preparó a partir del Ejemplo DSTL-1, etapa ha, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa (0 - 50% de B) en un gradiente de 25 min a 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) en la que el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. %). Se aisló el Ejemplo DSTL-1 (70.4 mg, 67.7%) en forma de un sólido blanco. RMN de ^1H (MeOD, 500 MHz, δ): 8.47 (d, *J* = 8.6 Hz, 1H), 8.44 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 1H), 5.34-5.31 (m, 1H), 5.07 (t, *J* = 7.32 Hz, 1H), 4.61 - 4.58 (m, 2H), 3.39-3,31 (m, 1H), 3.75-3.72 (m, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.83-2.81 (m, 1H), 2.64-2.59 (m, 1H), 2.49-2.48 (m, 2H), 2.23-2.14 (m, 3H), 2.05-2.03 (m, 1H), 1.18-1.12 (m, 2H), 1.05-0.92 (m, 13H), 0.83-0.81 (m, 1H). EM/CL (Cond.-D4): Tr = 2.24 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_{50}ClN_8O_6$: 821.36; encontrado 821.54.

Ejemplo *DSTL-2*

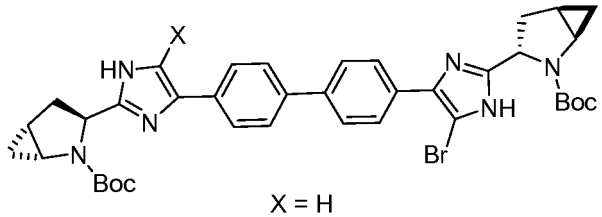


El Ejemplo DSTL-2 se preparó a partir del Ejemplo DSTL-1, etapa ha, de acuerdo con el procedimiento descrito para la purificación del Ejemplo GE2 a excepción de que se usa ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en lugar de Cap-51. La purificación se realizó mediante HPLC preparativa (0 - 50% de B) en un gradiente de 25 min a 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) en la que el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se aisló el Ejemplo DSTL-2 (18.0 mg) en forma de un sólido blanco. EM/CL (Cond.-D4): TR = 2.04 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{48}H_{54}ClN_8O_6$: 905.38; encontrado 905.60.

Ejemplo*s DSTL-3 y DSTL-4*



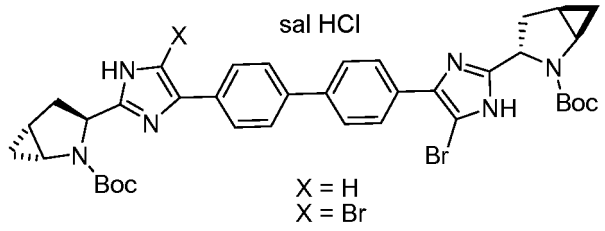
Ejemplo *DSTL-3, etapa a y DSTL-4, etapa a*



X = H
X = Br

Una solución de bromo (0.079 ml, 1.4 mmol) e AcOH (1 ml) se añadió en porciones a una solución agitada del Ejemplo 1, etapa d (1.0 g, 1.541 mmol) en AcOH (40 ml), y la mezcla se agitó a temperatura ambiente durante 3 horas. El disolvente se eliminó al vacío y el residuo se suspendió en DMC y se lavó con solución de $NaHCO_3$ saturado. La capa acuosa se extrajo dos veces más con DCM y los extractos orgánicos combinados se lavaron con salmuera y se secaron (Na_2SO_4). El residuo se cargó (DCM) en un cartucho Thompson de gel de sílice (160 g) y eluyeron con 30 - 100% de B en 2 l. Segmento 2: Conservación 100% de B para 800 ml. A/B Hexanos/EtOAc. Se aislaron 3 componentes; Material de partida (303.6 mg); Ejemplo DSTL-3, etapa a (X = H; 382.1 mg); sólido amarillo EM/CL (Cond.-D4): TR = 2.21 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{38}H_{44}BrN_6O_4$: 729.26; encontrado: 729.28; Ejemplo DTSL-4, etapa a (X = Br; 287.2 mg); sólido amarillo claro. EM/CL (Cond.-D4): TR = 2.62 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{38}H_{43}Br_2N_6O_4$: 807.17; encontrado: 807.33.

Ejemplo *DSTL-3, etapa b y DSTL-4, etapa b*



Los productos del Ejemplo DSTL-3, etapa b y DSTL-4, etapa b se realizaron por separado. La eliminación de los grupos protectores se efectuó tal como se ha descrito en el procedimiento del Ejemplo DSTL-1, etapa h.

X = H; Ejemplo DTSL-3, etapa b: Sólido amarillo, 33.1 (pureza del 97%); EM/CL (Cond.-D4): Tr = 1.49 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{28}H_{28}BrN_6$: 529.16; encontrado 529.24.

X = Br; Ejemplo DTSL-4, etapa b: Sólido amarillo, 33 mg (pureza del 96%); EM/CL (Cond.-D4): Tr = 1.82 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{28}H_{27}Br_2N_6$: 607.07; encontrado 607.16.

Ejemplo DSTL-3

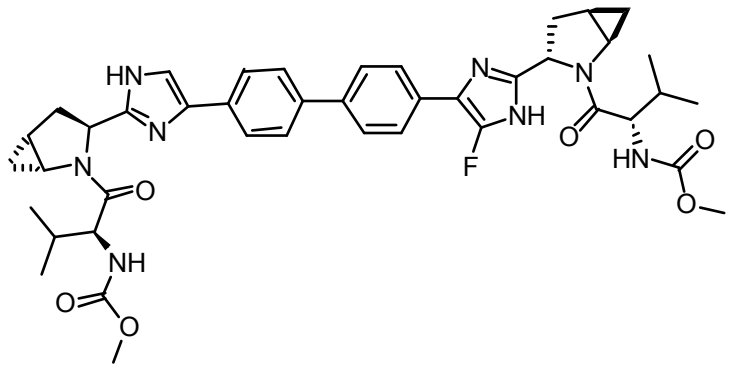
El Ejemplo DSTL-3 se preparó a partir del Ejemplo DSTL-3, etapa b, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa; (0 -50% de B) en un gradiente de 30 min a 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se aisló el Ejemplo DSTL-3 (29.0 mg) en forma de un sólido

blanco. EM/CL (Cond.-D4): Tr = 2.07 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{50}BrN_8O_6$: 843.30; encontrado 843.39.

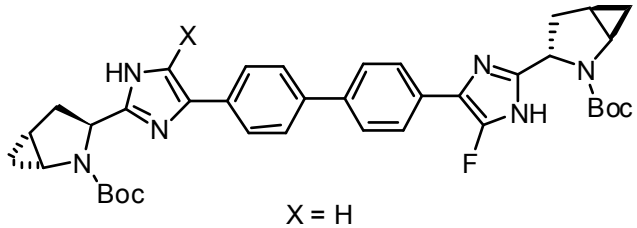
Ejemplo *DSTL-4*

El Ejemplo DSTL-4 se preparó a partir del Ejemplo DSTL-4, etapa b, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa; (0 -50% de B) en un gradiente de 30 min a 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) B = CH_3CN al 90% - H_2O al 10% – TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se aisló el Ejemplo DSTL-4 (30.2 mg) en forma de un sólido blanco. RMN al ^1H (MeOD, 500 MHz, δ): 7.82 (s, 8H), 5.08-5.05 (m, 2H), 4.58 (app d, *J* = 6.7 Hz, 2H), 3.76-3.74 (m, 2H), 3.67 (s, 6H), 2.57-2.52 (m, 2H), 2.50-2.44 (m, 2 H), 2.22-2.17 (m, 2H), 2.06-2.01 (m, 2H), 1.12-1.08 (m, 2H), 1.04 (d, *J* = 6.7 Hz, 6H), 0.95 (d, , *J* = 6.7 Hz, 6H), 0.84-0.82 (m, 2H). EM/CL (Cond.-D4): Tr = 2.56 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{42}H_{49}BrN_8O_6$: 921.31; encontrado 921.30.

Ejemplo *DSTL-5*



Ejemplo *DSTL-5, etapa a*



X = H
X = F

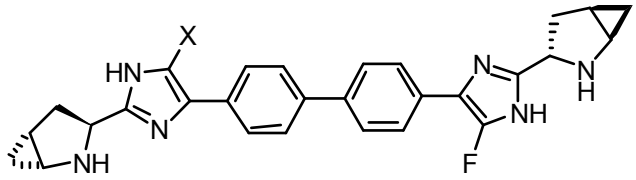
Se añadió Accufluor (al 45-50% en alúmina) (345 mg, 1.2 mmol) en una parte a una suspensión agitada del Ejemplo 1, Etapa d, 3.3'-(5.5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-azabiciclo[3.1.0]hexano-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-terc-butilo (500 mg, 0.77 mmol) en DMF seco (5 ml) a ta. La mezcla se situó dentro de un baño de aceite precalentado a 60°C y se agitó 4 h antes de que el disolvente se retirara por evaporación rotatoria en alto vacío. El producto en bruto se cargó a un cartucho de gel de sílice de Thompson de 90 g y eluyó del 10 – 100% de B en 2 litros y se mantuvo B al 100% B para 1 l (disolvente B = EtOAc; disolvente A = hexanos). Un segundo gradiente se aplicó eluyendo 0 – 100% de B en 2 litros (disolvente B = metanol; disolvente A = EtOAc). Se recogieron tres fracciones: Ejemplo DSTL-5, etapa a (X=F), 3.3'-(5.5'-(bifenil-4,4'-diil)bis(4-fluoro-1H-imidazol-5,2-diil))bis(2-azabiciclo[3.1.0]hexano-2-carboxilato) de (1R,1'R,3S,3'S,5R,5'R)-terc-butilo (45.0 mg, al 7%) como un sólido amarillo; Ejemplo DSTL-5, etapa a (X=H) 3-(5-(4'-(2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-

3-il)-1H-imidazol-5-il)bifenil-4-il)-4-fluoro-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de ((1R,3S,5R)-terc-butilo (193 mg, al 32%) como un sólido amarillo y recuperó el material de partida (153 mg, al 24%).

Ejemplo DSTL-5, etapa a X = F: una muestra (~10 mg) del primer compuesto que eluye se purificó adicionalmente por HPLC preparativa (B al 0 - 100%) durante un gradiente de 30 minutos (@ 40 ml/min) usando una columna Phenomenex Luna (30 x 100 mm, 10u) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95%- TFA al 0.1%. Se hubo aislado (4.6 mg) como un sólido amarillo claro. CL/EM (Cond.-D4): Tr = 4.43 min. CL/EM anal. calcd. para $[M+H]^+$ $C_{38}H_{43}F_2N_6O_4$: 685.33; encontrado 685.38.

Ejemplo DSTL-5, etapa a X = H: una muestra (~15 mg) del segundo compuesto que eluyese purificó adicionalmente por HPLC preparativa (B al 0 - 100%) durante un gradiente de 30 minutos (@ 40 ml/min) usando una columna Phenomenex Luna (30 x 100 mm, 10 u) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado (11.2 mg) como un sólido blanquecino. CL/EM (Cond.-D4): Tr = 4.43 min. CL/EM anal. calcd. durante $[M+H]^+$ $C_{38}H_{44}FN_6O_4$: 667.34; encontrado 667.40.

Ejemplo *DSTL-5, etapa b*



X = H
X = F

Los productos de Ejemplo DSTL-5, etapa a, (X = F) y (X = H), se llevaron adelante por separado. La eliminación de los grupos protectores se llevó a cabo como se describe en el procedimiento del Ejemplo DSTL-1, etapa h.

Ejemplo DTSL-5, etapa b (X = F): sólido amarillo, 23.4 mg; CL/EM (Cond.-D4): Tr = 2.89 min. CL/EM anal. calcd. para $[M+H]^+$ $C_{28}H_{27}F_2N_6$: 485.22; encontrado 485.25.

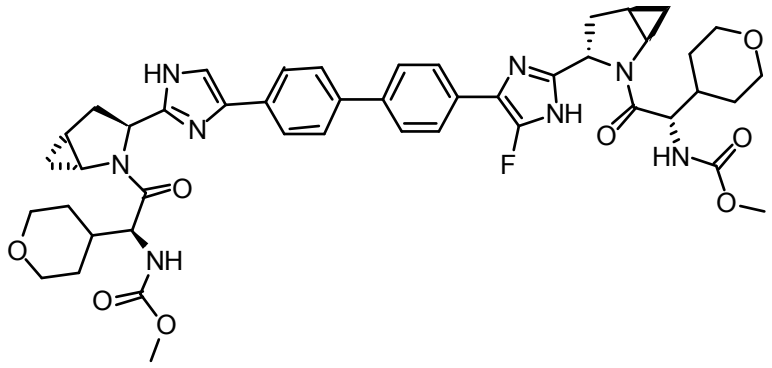
Ejemplo DTSL-5, etapa b (X = H): 18 mg (puro al 95%); CL/EM (Cond.-D4): Tr = 2.55 min. CL/EM anal. calcd. para $[M+H]^+$ $C_{28}H_{28}FN_6$: 467.25; encontrado 467.27.

Ejemplo *DSTL-5*

Se preparó el ejemplo DSTL-5 a partir del ejemplo DSTL-5, etapa b (X = H) según el procedimiento descrita para la preparación del Ejemplo GW2. La purificación se llevó a cabo por HPLC preparativa; 0% - 50%B en un gradiente de 30 min @ 40ml/min usando una columna de Waters-SunFire (30 x 100 mm, S5) B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-5 (37.3 mg, al 39%) como un sólido amarillo pálido. RMN de ^1H (MeOD, 500 MHz, δ): 7.88 (s, 1 H), 7.84

(d, *J=8.5* Hz, 2H), 7.80 (d, *J=8.5* Hz, 2H), 7.77 (d, *J=8.5* Hz, 2H), 7.68 (d, *J=8.5*, 2H), 5.13 (t, *J=7.0* Hz, 1H), 5.04 (t, *J= 6.1*Hz, 1H), 4.56 (d, *J= 6.7* Hz, 2H) 3.82 (s ancho, 1H), 3.68-3.67 (m, 7H), 2.72-2.68 (m, 1H), 2.51-2.43 (m, 3H), 2.21-2.14 (m, 2H), 2.09 (s ancho, 1H), 2.03 (s ancho, 1H), 1.15-1.09 (m, 2H), 1.02 (d, *J=6.7* Hz, 6H), 0.94 (t, J=7.0 Hz, 6H), 0.90 (s ancho, 1H), 0.81 (s ancho, 1H). CE/EM (Cond-D4): RT = 3.45 min. CL/EM Anal. Calc. para $[M+H]^+$ $C_{42}H_{50}FN_8O_6$: 781.39; encontrado 781.54.

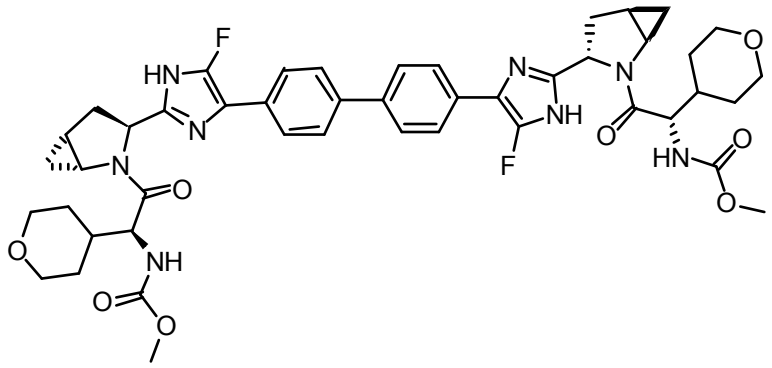
Ejemplo *DSTL-6*



Se preparó el Ejemplo DSTL-6 a partir del Ejemplo DSTL-5, etapa b (X = H) según el procedimiento descrito para la preparación del Ejemplo GW2 salvo usando ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en vez de *Cap-51*. La purificación se llevó a cabo por HPLC preparativa (B al 0 - 50%) en un gradiente de 25 minutos (@ 40ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se ha

aislado el Ejemplo DSTL-6 (37.1 mg, al 36%) en forma de un sólido blanco. CL/EM (Cond.-D4): Tr = 3.17 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{48}H_{54}FN_8O_6$: 865.41; encontrado 865.55.

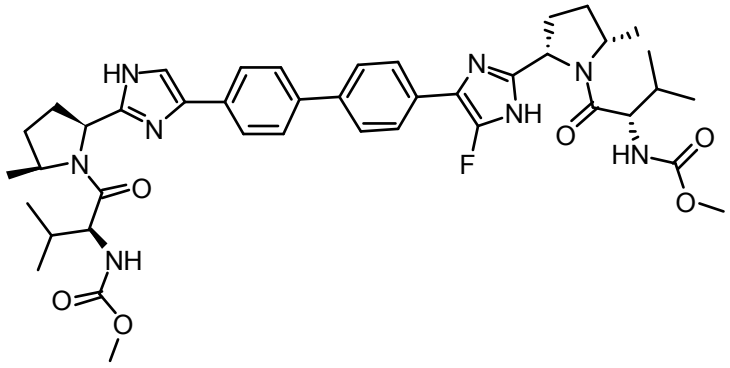
Ejemplo *DSTL-7*



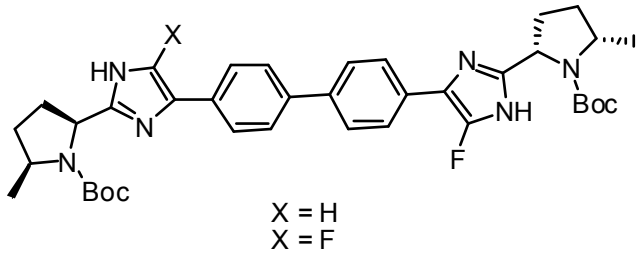
Se preparó el Ejemplo DSTL-7 a partir del Ejemplo DSTL-5, etapa b (X = F) según el procedimiento descrito para la preparación del Ejemplo GW2 salvo usando ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en vez de *Cap-51*. La purificación se llevó a cabo por HPLC preparativa (B al 0 - 50%) en un gradiente de 25 min (@ 40ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado el Ejemplo DSTL-7 (14 mg, al 25%) en forma de un sólido blanco. RMN de ^1H (MeOD, 500 MHz, δ) 7.72 (d, *J=8.5* Hz, 4H), 7.64 (d, *J=8.5* Hz, 4H), 5.03 (t, *J=6.7* Hz, 2H), 4.63 (d, *J= 7.6* Hz, 2H), 3.97-3.93 (m, 4H), 3.72 (s ancho, 2H), 3.67 (s, 6H), 3.42-3,37 (m, 4H), 2.44-2.42 (m, 4H), 2.02 (s ancho, 4H),1.63-1.57 (m, 6H), 1.46-1.43 (m, 2H), 1.14-1.19

(m, 2H), 0.80 (s ancho, 2H): CL/EM (Cond.-D4): Tr = 3.17 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{46}H_{53}F_2N_8O_6$: 883.40; encontrado 883.57.

Ejemplo *DSTL-8*



Ejemplo DSTL-8, etapa a

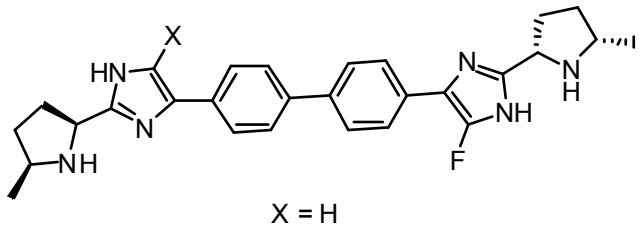


X = H
X = F

Se añadió Accufluor (al 45-50% en alúmina) (274 mg, 0.92 mmol) en una parte a una suspensión agitada de Ejemplo GW1, Etapa a, 5.5'-(5.5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpirrolidina-1-carboxilato) de (2S,2'S,5S,5'S)-terc-butilo (400 mg, 0.6 mmol) en DMF seco (4 ml) a ta. La mezcla se situó en un baño de aceite precalentado a 60°C y se agitó 4 horas antes de que se añadan 135 mg adicionales de Accufluor y se siguieron agitando a 60°C durante 16 h. El disolvente se retiró por evaporación rotatoria en alto vacío y el producto en bruto se cargó en un cartucho de gel de sílice de 90 g Thompson y eluyó del 10 –

100% de B en 2 litros y se mantuvo B al 100% para 1 l (disolvente B = EtOAc; disolvente A = hexanos). Se aplicó un segundo gradiente eluyendo B al 0 – 100 % en 2 l (disolvente B = metanol; disolvente A = EtOAc). Se recogieron tres fracciones: Ejemplo DSTL-8, etapa a (X = F), 5.5'-(5.5'-(bifenil-4,4'-diil)bis(4-fluoro-1H-imidazol-5,2-diil))bis(2-metilpirrolidina-1-carboxilato) de (2S,2'S,5S,5'S)-terc-butilo (33 mg, al 5.1%) en forma de un sólido naranja amarillento. CL/EM (Cond.-D4): Tr = 4.64 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{38}H_{47}F_2N_6O_4$: 689.36; encontrado 689.50. Ejemplo DSTL-8, etapa a (X = H) 2-(5-(4'-(2-((2S,5S)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-4-fluoro-1H-imidazol-2-il)-5-metilpirrolidine-1-carboxilato de (2S,5S)-terc-butilo (108.6 mg, al 17%) en forma de un sólido naranja amarillento. CL/EM (Cond.-D4): Tr = 3.83 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{38}H_{48}FN_6O_4$: 671.37; encontrado 671.48 y se recuperó el material de partida (321.2 mg, al 80%) como un sólido naranja rojizo.

Ejemplo *DSTL-8, etapa b*



X = H
X = F

Los productos del Ejemplo DSTL-8, etapa a, (X = F)

y (X = H), se llevaron adelante por separado. La eliminación de los grupos protectores se llevó a cabo como se describe en el procedimiento del Ejemplo DSTL-1, etapa h.

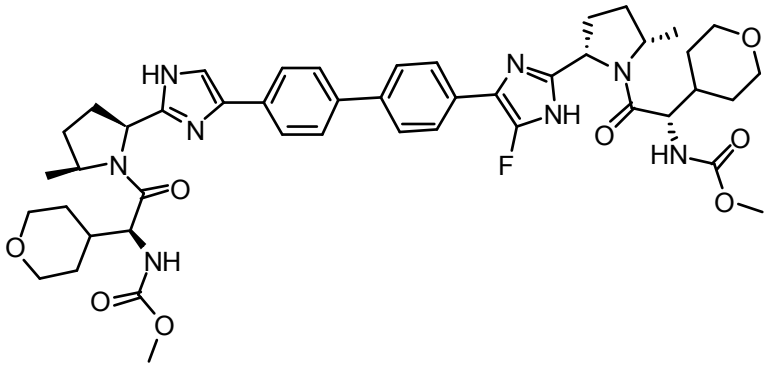
Ejemplo DTSL-8, etapa b (X = F): sólido amarillo, 22.7 mg; CL/EM (Cond.-D4): Tr = 3.03 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{28}H_{30}F_2N_6$: 489.26; encontrado 489.35.

Ejemplo DTSL-8, etapa b (X = H): 35 mg (puro al 95%); CL/EM (Cond.-D4): Tr = 2.63 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{28}H_{31}FN_6$: 471.27; encontrado 471.33.

Ejemplo *DSTL-8*

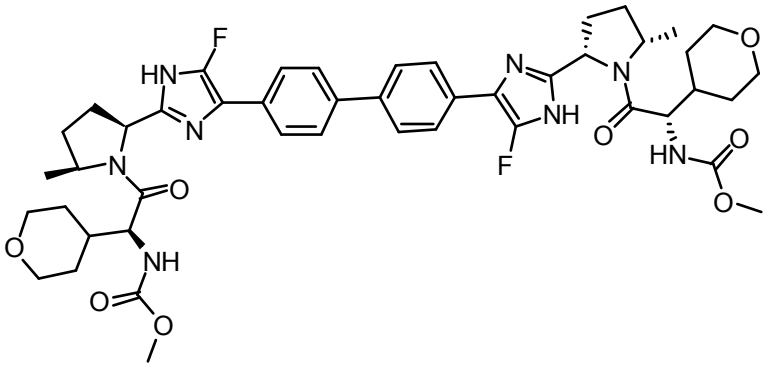
El Ejemplo DSTL-5 se preparó a partir del Ejemplo DSTL-8, etapa b (X = H) según el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se llevó a cabo por HPLC preparativa; 0% - 50% de B en un gradiente de 30 min @ 40 ml/min usando una columna Waters-SunFire (30 x 100 mm, S5) B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-8 (31.9 mg, al 41%) como un sólido de color melocotón claro. CL/EM (Cond-D4): Tr = 3.66 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{42}H_{54}FN_8O_6$: 785.42; encontrado 785.48.

Ejemplo *DSTL-9*



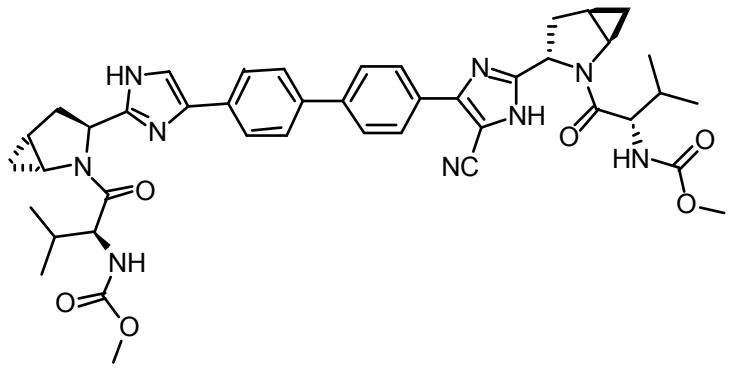
El Ejemplo DSTL-9 se preparó a partir del Ejemplo DSTL-8, etapa b (X = H) de acuerdo al procedimiento descrito para la preparación del Ejemplo GW2 salvo usando ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en vez de *Cap-51*. La purificación se llevó a cabo por HPLC preparativa (B al 0 - 50%) en un gradiente de 25 min (@ 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-9 (27.2 mg, al 32%) en forma de un sólido amarillo pálido. CL/EM (Cond.-D4): Tr = 3.37 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{46}H_{58}FN_8O_8$: 869.44; encontrado 869.54.

Ejemplo *DSTL-10*

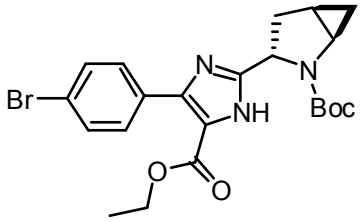


El Ejemplo DSTL-10 se preparó a partir del Ejemplo DSTL-8, etapa b (X = F) según el procedimiento descrito para la preparación del Ejemplo GW2 salvo porqué usa ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en vez de *Cap-51*. La purificación se llevó a cabo por HPLC preparativa (B al 0 - 50%) en un gradiente de 25 min (@ 40ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) donde el disolvente B = CH_3CN 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-10 (13.8 mg, al 25%) como un sólido amarillo pálido. CL/EM (Cond.-D4): Tr = 4.28 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{46}H_{57}F_2N_8O_8$: 887.43; encontrado 887.50.

Ejemplo DSTL-11

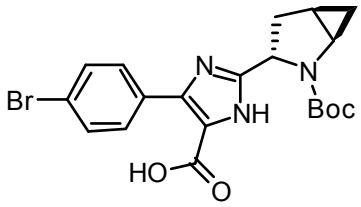


Ejemplo *DSTL-11, etapa a*



La preparación de DSTL-11, etapa a, se llevó a cabo en modi análogo al compuesto J5 en solicitud de patente 20080213 US 10889A USCIP. CL/EM (Cond.-D4): Tr = 2.22 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{22}H_{27}BrN_3O_4$: 476.12; encontrado 478.17.

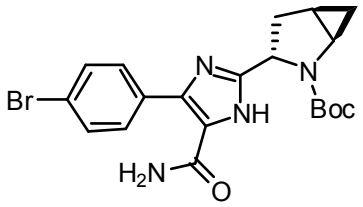
Ejemplo *DSTL-11, etapa b*



Se añadió hidróxido de sodio 5N (1.469 ml, 7.4 mmol) a una solución de DSTL-11, etapa a 3-(4-(4-bromofenil)-5-(etoxicarbonil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-tert-butilo (1.75 g, 3.7 mmol) en etanol (40 ml). La mezcla se agitó a 50°C durante 16 horas y se añadió NaOH 5N adicional (1.5 ml). La mezcla se agitó a 60°C durante 6 h y se añadió NaOH 5N adicional (0.75 ml) y la agitación se continuó a 60°C durante 16 h. El etanol se retiró por evaporación rotatoria y el residuo se llevó en acetato de etilo y se neutralizó a pH = 5 (HCl 1 N aprox. 20 ml hasta que se cierra a pH = 7, después con regulador de pH fosfato pH =5). La fase orgánica

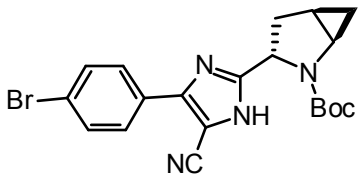
se seàró, se lavó con salmuera, se secó y se concentró. Se hubo aislado Ejemplo DSTL-11, etapa b (1.6 g, al 92%) en forma de un sólido blanco. CL/EM (Cond.-D4): Tr = 1.78 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{20}H_{22}BrN_3O_4$: 448.09; encontrado 447.97.

Ejemplo *DSTL-11, etapa c*



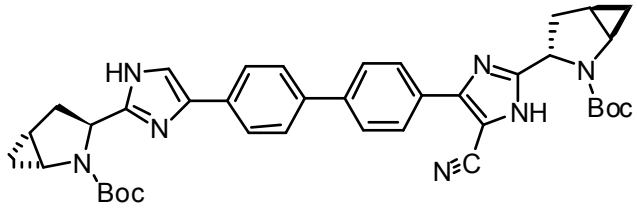
Se añadió CDI (0.58 g, 3.57 mmol) en una parte a una solución agitada de DSTL-11, etapa b, 4-(4-bromofenil)-2-((1R,3S,5R)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-5-carboxílico (1.6 g, 3.57 mmol) en THF seco (30 ml). La mezcla se agitó a 50°C durante 4 h antes de enfriarse a ta y se añadió NH_4OH (conc.) (4.96 ml, 35.7 mmol). La mezcla se agitó durante 16 horas antes, se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada, salmuera y se secó. El producto en bruto se cargó a un cartucho de gel de sílice de 160 g de Thompson y eluyó 40 - 100% de B en 3 l, seguido por una retención a B al 100% para 1 l. (Disolvente B = EtOAc; disolvente A = hexanos). Se hubo aislado Ejemplo DSTL-11, etapa c, (1.76 g, al 99%). CL/EM (Cond.-D4): Tr = 1.75 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{20}H_{24}BrN_4O_3$ 449.10; encontrado: 449.06.

Ejemplo *DSTL-11, etapa d*



Se añadió 2,4,6-tricloro-1,3,5-triazina (cloruro cianúrico) (168 mg, 0.91 mmol) en una parte a una solución agitada de 3-(4-(4-bromofenil)-5-carbamoil-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo (903 mg, 1.82 mmol) en DMF seco (4 ml). La mezcla se agitó durante 2 horas y después se calentó a 50°C durante 16 h. Se añadió cloruro cianúrico (20 mg) y la mezcla se agitó adicionalmente a 50°C durante 24 horas, se diluyó con EtOAc y agua y la fase orgánica se lavó con solución de $NaHCO_3$ saturada, salmuera y se secó (Na_2SO_4). El producto en bruto se cargó a un cartucho de gel de sílice de 90 g de Thompson y se eluyó 25 -100% B en 1.5 l, seguido por una retención a B al 100% para 500 mL. (Disolvente B = EtOAc; disolvente A = hexanos). Se hubo aislado Ejemplo DSTL-11, etapa d, (346 g al 60%) como una espuma canela amarillenta. CL/EM (Cond.-D4): Tr = 3.93 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{20}H_{22}BrN_4O_2$ 431.09; encontrado: 431.01.

Ejemplo *DSTL-11, etapa e*



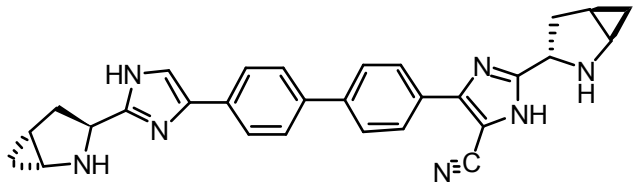
Se añadió tetrakis(trifenil)paladio (45.8 mg, 0.04

mmol) a una suspensión purgada con argon de Ejemplo DSTL-11, etapa d, 3-(5-(4-bromofenil)-4-ciano-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo (340 mg, 0.79 mmol), 3-(4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hexano-2-carboxilato de (1R,3S,5R)-terc-butilo (393 mg, 0.871 mmol) y $NaHCO_3$ (333 mg, 3.96 mmol) en DME (6 ml) y agua (1.5 ml) en un tubo de paredes gruesas, coronado por un tornillo. La mezcla de reacción se purgó por flujo con argón, se selló y se sumergió en un baño de aceite precalentado (80°C) y se agitó 14 h. La mezcla se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada, salmuera, se secó sobre (Na_2SO_4). El producto en bruto se cargó a un cartucho de gel de sílice de 90 g Thompson y se eluyó con 35 – 100% de B en 1.5 l, seguido por retención a B al 100% para 0.5 l. (Disolvente B = EtOAc; disolvente A = hexanos). Se hubo aislado Ejemplo DSTL-11, etapa e, (200 mg, al 36%) como una espuma amarilla clara.

Una muestra pequeña (~20 mg) se sometió a purificación adicional por HPLC prep. (B al 0% a B al 100% en un gradiente de 25 minutos @ 40 ml/min) usando una columna Phenomenex Gemini (30 x 100 mm, 10u) donde el disolvente B = CH_3CN al 95% - H_2O al 5% - NH_4OAc 10 mM y A = CH_3CN al 5% - H_2O al 95% - NH_4OAc 10 mM (12.9 mg). CL/EM (Cond.-D4): Tr = 3.51 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{39}H_{44}N_7O_4$ 674.35;

encontrado: 674.29.

Ejemplo *DSTL-11, etapa f*



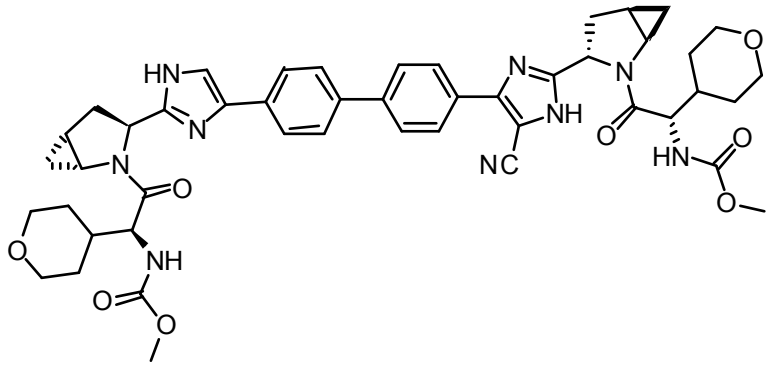
El producto de Ejemplo DSTL-11, etapa f se obtuvo tras eliminación de los grupos protectores según se describen en el procedimiento del Ejemplo DSTL-1, etapa h. CL/EM (Cond.-D4): Tr = 2.36 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{29}H_{28}N_7$: 474.24; encontrado 474.13.

Ejemplo *DSTL-11*

El Ejemplo DSTL-11 se preparó a partir de Ejemplo DSTL-11, etapa f de acuerdo con el procedimiento descrito para la preparación de Ejemplo GW2. La purificación se llevó a cabo por HPLC preparativa; 0% - 50% de B en un gradiente de 30 min @ 40ml/min usando una columna Waters-SunFire (30 x 100 mm, S5) B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-11 (21.5 mg, al 31%) como un sólido blanco. RMN de ^1H (MeOD, 500 MHz, δ): 7.93-7.82 (m, 9 H), 5.15-5.08 (m, 2H), 4.58 – 4.56 (m, 2H), 3.82 (s ancho, 1H), 3.72 (s ancho, 1H) 3.67 (s, 6H), 2.73-2.67 (m, 1H), 2.50-2.46 (m, 3H), 2.21-2.14 (m, 2H), 2.09 (s ancho, 1H), 2.03 (s ancho, 1H),

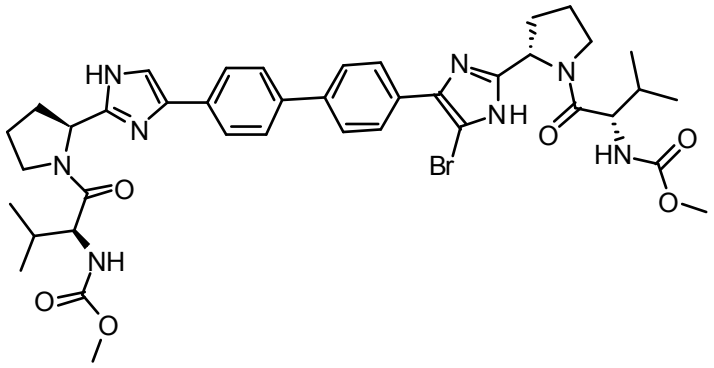
1.14-1.10 (m, 2H), 1.05 – 1.02 (m, 6H), 0.97-0.93 (m, 6H), 0.90 (s ancho, 1H), 0.83 (s ancho, 1H). CL/EM (Cond-D4): Tr = 3.25 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{43}H_{50}N_9O_6$: 780.39; hallado 788.31.

Ejemplo *DSTL-12*

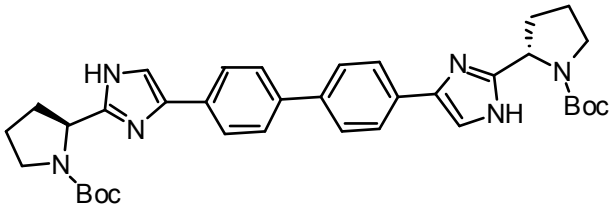


Se preparó Ejemplo DSTL-12 a partir de Ejemplo DSTL-11, etapa f según el procedimiento descrito para la preparación de Ejemplo GW2 salvo porque usa (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético en vez de *Cap-51*. La purificación se llevó a cabo por HPLC preparativa (B al 0 - 50%) en un gradiente de 25 min (@ 40 ml/min) usando una columna Waters-SunFire (30 x 100 mm, S5) donde el disolvente B = CH_3CN al 90% - H_2O al 10% - TFA al 0.1% y A = CH_3CN al 5% - H_2O al 95% - TFA al 0.1%. Se hubo aislado Ejemplo DSTL-12 (26.7 mg, al 35%) como un sólido blanquecino. CL/EM (Cond.-D4): Tr = 2.98 min. CL/EM Anal. calcd. para $[M+H]^+$ $C_{47}H_{54}N_9O_8$: 872.41; encontrado 872.35.

Ejemplo *JLR-1*

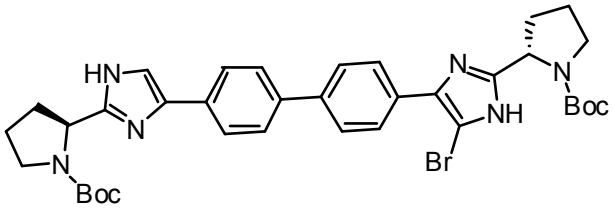


Ejemplo *JLR-1, etapa a*



Para la síntesis del Ejemplo JLR-1, etapa a, véase el procedimiento de la solicitud de patente WO2009/020825.

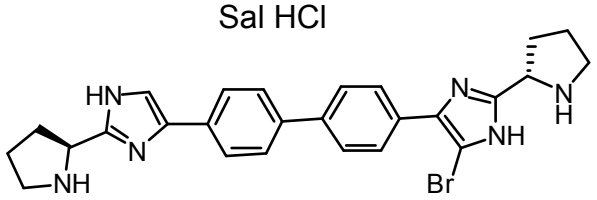
Ejemplo *JLR-1, etapa b*



Una solución de bromo 1M en AcOH (0.4 ml) se añadió a una solución del Ejemplo JLR-1, etapa a (250 mg, 0.40 mmol) en ácido acético (15 ml) y se agitó durante 3 horas. La mezcla de reacción se vertió DCM (100 ml) y se trató con solución de $NaHCO_3$ saturado hasta un pH = neutro. La fase orgánica se concentró y se secó al vacío. La reacción dio una mezcla 1:1:1 del material de partida: monobromuro: dibromuro, que se separaron tras la aplicación (DCM) a una

columna Thompson de SiO_2 (25 g). La elución (Biotage) por gradiente 15 - 100% de B en 500 ml dio el Ejemplo JLR-1, etapa b (180 mg). EM/CL (Cond. J4 TR = 2.75 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{36}H_{44}BrN_6O_4$: 705.26; encontrado 705.22.

Ejemplo *JLR-1, etapa c*

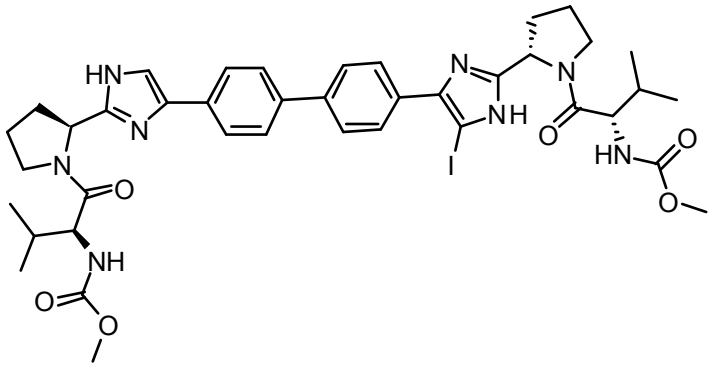


Una solución de HCl 4N en dioxano (4 ml) se añadió al ejemplo JLR-1, etapa b (38 mg, 0.054 mmol) en MeOH (4 ml) y se agitó durante 4 h. El disolvente se eliminó al vacío y la sal tetra HCl se secó en alto vacío. EM/CL (Cond. J4 TR = 1.75 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{26}H_{28}BrN_6$: 503.16; encontrado 503.26.

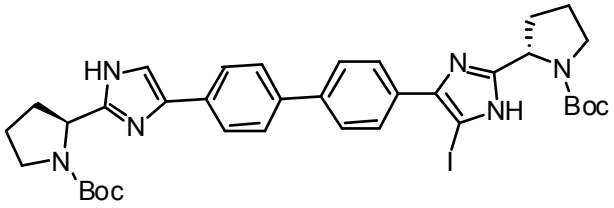
Ejemplo *JLR-1*

El Ejemplo JLR-1 se preparó a partir del Ejemplo JLR-1, etapa c, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa en columna phenonmenex-Luna (30 x 100 mm S10) con un gradiente de 25 min de 15-100% de B a 40 ml/min), en la que el disolvente B = MeOH al 90%- H_2O al 10% – TFA al 0.1% y A = MeOH al 5% - H_2O al 95% - TFA al 0.1%. EM/CL (Cond. J4): Tr = 2.61 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{50}BrN_8O_6$: 819.31; encontrado 819.23.

Ejemplo *JLR-2*

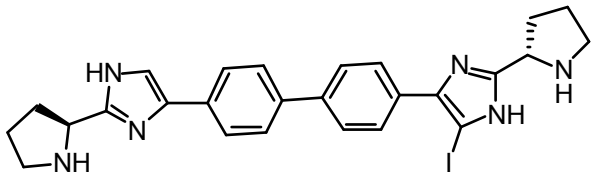


Ejemplo *JLR-2, etapa a*



A una solución del Ejemplo JLR-1, etapa a (400 mg, 0.640 mmol) y $NaHCO_3$ (161 mg, 1.921 mmol) en dioxano (15 ml) y agua (15 ml) se añadió yodo (162 mg, 0.640 mmol) y la reacción se agitó durante 6 horas con solución de $Na_2S_2O_3$ al 10% (40 ml) y se diluyó con EtOAc/THF (2:1). La fase orgánica se concentró y el producto bruto se aplicó (DCM) a una columna Thompson de gel de sílice (40 g) y eluyó con 35-100% de B en 1 l (A/B DCM/EtOAc), dando una mezcla del material de partida, diyoduro (255 mg) y el Ejemplo JLR-2, etapa a (46 mg, 9%). EM/CL (Cond. J4): Tr = 2.45 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{36}H_{44}IN_6O_4$: 751.24; encontrado 751.18.

Ejemplo *JLR-2, etapa b*



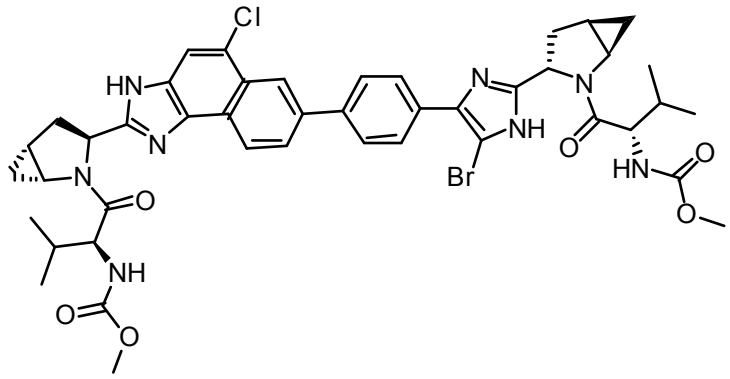
Sal HCl

Una solución de HCl 4N en dioxano (5 ml) se añadió al ejemplo JLR-2, etapa a (46 mg, 0.061 mmol) en MeOH (5 ml) y se agitó durante 5 h. El disolvente se eliminó al vacío y la sal tetra HCl se secó en alto vacío. EM/CL (Cond. J4): Tr = 1.70 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{26}H_{28}IN_6$: 551.13; encontrado 551.09.

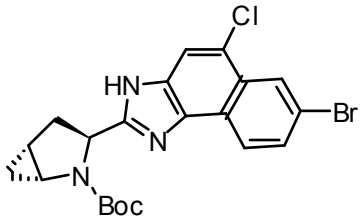
Ejemplo *JLR-2*

El Ejemplo JLR-2 se preparó a partir del Ejemplo JLR-2, etapa b, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC semipreparativa; en columna Dynamax 6A semi-prep C8 ; 5%-95% de B en 30 minutos a 20 ml/min), en la que el disolvente B = CH_3CN al 90% - H_2O al 10% - NH_4OAc al 1% y A = CH_3CN al 5% -H_2O al 95% - NH_4OAc al 1%. EM/CL (Cond. J4): TR = 2.35 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{50}IN_8O_6$: 865.29; encontrado 865.31.

Ejemplo JLR-3

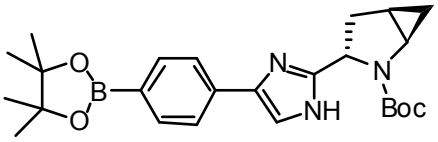


Ejemplo JLR-3, etapa a



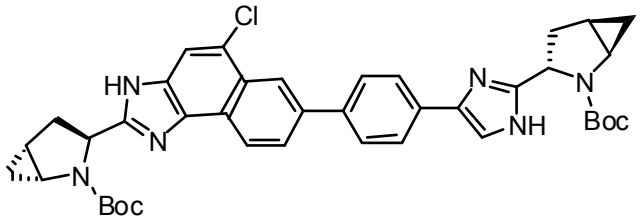
A una solución del Ejemplo DSTL-1, etapa d (510 mg, 1.191 mmol) en DMF (10 ml) se añadió NCS (175 mg, 1.310 mmol) y se agitó durante 18 horas a 50 °C. El disolvente se retiró mediante evaporación rotatoria en alto vacío y el residuo se cargó (DCM) en un cartucho Thompson de de gel de sílice (80 g). La elución por gradiente se realizó en 25 - 100% de B en 750 ml (A/B Hex/EtOAc), dando el Ejemplo JLR-3, etapa a (250 mg, 46%). ^{1}H-RMN (MeOD, 500 MHz, δ): 8.58 (s, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 7.97 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 4.98 (s, 1H), 3.70 (s, 1 H), 2.76-2.71 (m, 1H), 2.50-2.45 (m, 1H), 1.86 (s, 1H), 1.48/1.12 (s, 9H), 0.96-0.92 (m, 1H), 0.79-0.77 (m, 1H). EM/CL (Cond. J4): Tr = 3.13 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{21}H_{22}BrClN_3O_2$: 464.06; encontrado 464.05.

Ejemplo *JLR-3, etapa a.1*



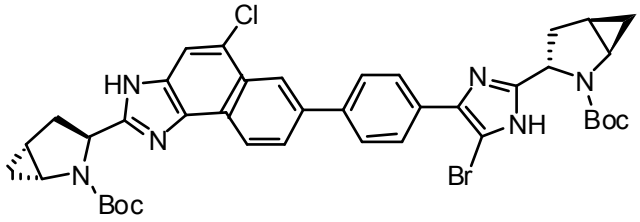
El Ejemplo JLR-3, etapa a.1 se preparó a partir del Ejemplo DSTL-1, etapa d.1, de acuerdo con el procedimiento descrito en la solicitud de patente WO2008/021927 para la preparación de su análogo desmetano.

Ejemplo *JLR-3, etapa b*



El Ejemplo JLR-3, etapa b, se preparó a partir del Ejemplo JLR-3, etapa a.1 de acuerdo con el procedimiento descrito para la preparación del Ejemplo DSTL-1, etapa g, dando el ejemplo JLR-3, etapa b. CL/EM (Cond. J4): Tr = 2.72 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{44}ClN_6O_4$: 707.31; encontrado 707.44.

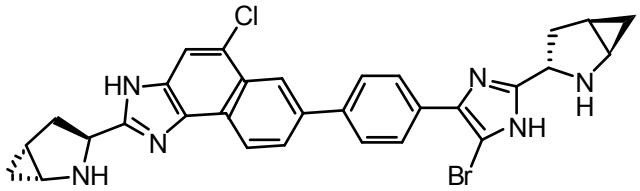
Ejemplo *JLR-3, etapa c*



El Ejemplo JLR-3, etapa c, se preparó a partir del Ejemplo JLR-3, etapa b de acuerdo con el procedimiento descrito para la preparación del Ejemplo DSTL-3, etapa a, dando el ejemplo JLR-3, etapa c. CL/EM (Cond. J4): Tr = 3.30

min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{43}BrClN_6O_4$: 787.21; encontrado 787.34.

Ejemplo *JLR-3, etapa d*



Sal HCl

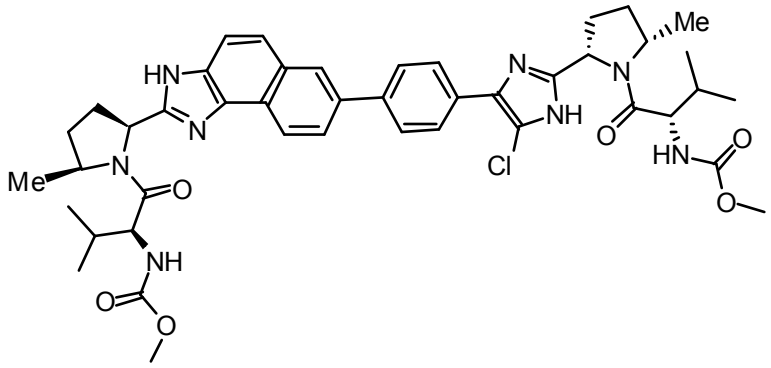
El Ejemplo JLR-3, etapa d, se preparó a partir del Ejemplo JLR-3, etapa c de acuerdo con el procedimiento descrito para la preparación del Ejemplo JLR-1, etapa b. CL/EM (Cond. J4): Tr = 2.37 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{30}H_{27}BrClN_{66}$: 587.12; encontrado 587.14.

Ejemplo *JLR-3*

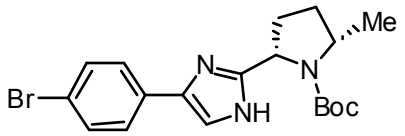
El Ejemplo JLR-3 se preparó a partir del Ejemplo JLR-3, etapa d, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa en columna phenonmenex-Luna (30 x 100 mm S10) con un gradiente de 18 min de 15-100% de B a 40 ml/min), en la que el disolvente B = MeOH al 90%- H_2O al 10% – TFA al 0.1% y A = MeOH al 5% - H_2O al 95% - TFA al 0.1%. ^{1}H-RMN (MeOD, 500 MHz, δ): 8.69-8.68 (m, 1H), 8.52-8.50 (m, 1H), 8.18-8.16 (m, 1H), 7.98-7.96 (m, 1H), 7.91-7.90 (m, 4H), 5.34-5.34 (m, 1H), 5.09-5.06 (m, 1 H), 4.62-4.58 (m, 2H), 3.91 (s ancho, 1H), 3.76 (s ancho, 1H) 3.69 (s, 6H), 2.77-2.73 (m, 1H), 2.64-2.59 (m, , 1H), 2.51-2.48 (m, 2H),

2.23-2.16 (m, 3H), 2.06 (s ancho, 1H), 1.17-1.12 (m, 2H), 1.06-0.92 (m, 13H), 0.83 (m, 1H). EM/CL (Cond. J4): Tr = 3.14 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{44}H_4BrClN_8O_6$: 901.27; encontrado 901.45.

Ejemplo *JLR-4*



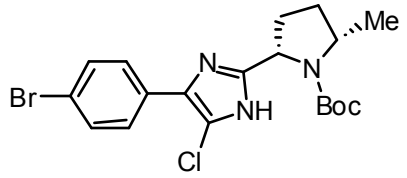
Ejemplo *JLR-4, etapa a*



A una solución de 2-bromo-1-(4-(bromofenil)etanona (2.5 g, 8.99 mmol) y ácido (2S,5S)-1-(terc-butoxicarbonil)-5-metilpirrolidin-2-carboxílico (1.9 g, 8.29 mmol) en acetonitrilo (75ml) se añadió base de Hunig (1.2 g, 9 mmol) y se agitó durante 6 horas a 24°C. La mezcla reacción se concentró y el residuo se suspendió en EtOAc y se lavó con agua. La concentración dio un sólido blanco que se suspendió en xileno (90 ml). Se añadió acetato amónico (4.23 g, 70.4 mmol) y la solución se agitó en un vaso a presión con tapa de rosca a 135 °C durante 3.5 horas. La mezcla de reacción se diluyó con EtOAc (400 ml) y se lavó con solución

de $NaHCO_3$ saturado y se concentró. El producto en bruto se cargó (DCM) hasta 80 g en un cartucho de gel de sílice Thompson y se realizó la elución por gradiente del 15 - 100% de B en 1 l (A/B Hex/EtOAc) dando el Ejemplo JL3-4, etapa a (rendimiento no determinado). EM/CL (Cond. J4): Tr = 2.21 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$: 406.12; encontrado 406.10. [Nota: para la preparación del ácido carboxílico de partida, véase la solicitud de patente US 2009/0068140)

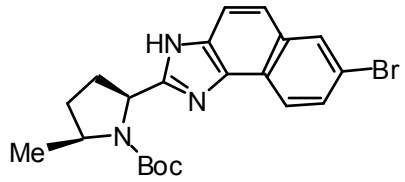
Ejemplo JLR-4, etapa b



A una solución del Ejemplo JLR-4, etapa a (700 mg, 1.7 mmol) en DMF (10 ml) se añadió NCS (161 mg, 1.21 mmol) y se agitó durante 18 horas a 50 °C. Se añadió NCS adicional (50 mg) y la reacción continuó durante 6 horas antes de eliminar el disolvente mediante purga con nitrógeno. El producto en bruto se cargó (DCM) hasta 40g en un cartucho de gel de sílice Thompson y se realizó la elución por gradiente del 15 - 100% de B en 750 ml (A/B Hex/EtOAc) dando el Ejemplo JL3-4, etapa b (580 mg, 70%). ^{1}H-RMN (MeOD, 500 MHz, δ): 7.62 (appr s, 4H), 4.77 (br, s, 1H), 4.03 (br, s, 1H), 2.24 (s ancho, 2H), 2.16-2.11 (m, 1H) 1.79 (s ancho, 1H), 1.47-1,25 (m, 12H). EM/CL (Cond. J4): Tr = 3.33 min. CL/EM

Anal. Calculado para $[M+H]^+$ $C_{19}H_{24}BrClN_3O_2$: 440.08; encontrado 440.0.

Ejemplo JLR-4, etapa c

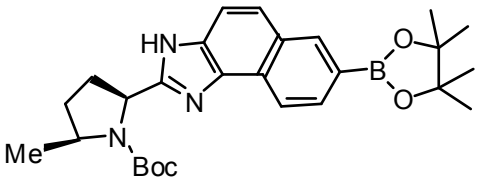


A una solución del Ejemplo DSTL-1, etapa c (1.6 g, 6.75 mmol) y ácido (2S,5S)-1-(terc-butoxicarbonil)metilpirrolidina-2-carboxílico (1.55 g, 6.75 mmol) en DCM (100 ml) y se agitó durante 6 horas. (Nota: La dianilina no era completamente soluble). La mezcla de reacción se diluyó con DCM (1 vol) y se lavó con solución $NaHCO_3$ semisaturada. La concentración dio un sólido (2.5 g). EM/CL (Cond. J4): TR = 3.07 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{21}H_{27}BrN_3O_3$: 448.13; encontrado 448.11.

El sólido bruto (2.5 g, 5.58 mmol) se suspendió en AcOH (200 ml) y se agitó durante 18 horas a 60 °C. La concentración en alto vacío eliminó el disolvente. El residuo se suspendió en DCM, se lavó con solución de $NaHCO_3$ saturado y se concentró. El residuo se cargó (DCM) en un cartucho Thompson de gel de sílice de 80 g y la elución por gradiente se realizó del 15 - 100% de B en 750 ml. (A/B Hex/EtOAc) dando el Ejemplo JLR-4, etapa c (2.6 g). RMN de ^1H (MeOD, 500 MHz, δ): 8.36-8.35 (m, 2H), 8.0 (d, *J* = 9Hz, 1H), 7.91 (dd, *J* = 9, 2 Hz, 1H), 7.87 (d, *J* = 9 Hz, 1H),

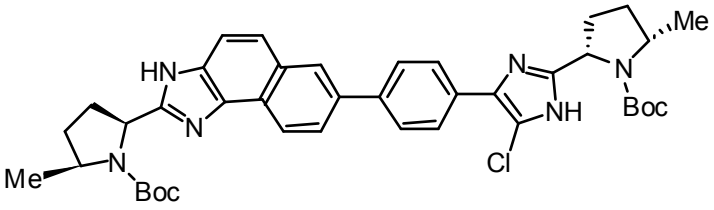
5.31-5.28 (m, 1H), 4.17 (br, s, 1H), 2.59-2.56 (m, 1H), 2.39-2.31 (m, 2H) 1.86-1.83 (m, 1H), 1.52-1.19 (m, 12H). EM/CL (Cond. J4): Tr = 2.57 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{21}H_{25}BrN_3O_2$: 430.12; encontrado 430.09.

Ejemplo *JLR-4, etapa d*



El Ejemplo JLR-4, etapa d, se preparó a partir del Ejemplo JLR-4, etapa c de acuerdo con el procedimiento descrito para la preparación del Ejemplo DSTL-1, etapa f. L/EM (Cond. J4): T_R = 2.86 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{27}H_{37}BN_3O_4$: 478.29; encontrado 478.25.

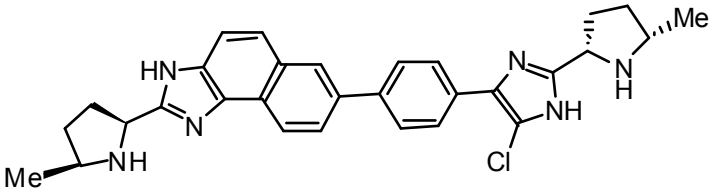
Ejemplo *JLR-4, etapa e*



El Ejemplo JLR-4, etapa e se preparó a partir del Ejemplo JLR-4, etapa d y el ejemplo JLR-4, etapa b, de acuerdo con el procedimiento descrito para la preparación del Ejemplo DSTL-1, etapa g, dando el Ejemplo JLR-4, etapa e. RMN de ^1H (MeOD, 500 MHz, δ): 8.53 (d, *J* = 8.6 Hz, 1H), 8.49 (s, 1H), 8.20 (dd, *J* = 8.6, 2 Hz, 2H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 1H), 5.32 (t, *J* = 6.4 Hz, 1H), 4.85 (br, s, 1H), 4.20 (s ancho,

1H), 4.06 (br, s, 1H), 2.59-2.58 (m, 1H), 2.44-2,28 (m, 4H), 2.19-2.15 (m, 1H), 1.89-1.84 (m, 1H), 1.83-1.79 (m, 1H), 1.54-1,20 (m, 24H). EM/CL (Cond. J4): Tr = 3.18 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{40}H_{48}ClN_6O_4$: 711.34; encontrado 711.31.

Ejemplo *JLR-4, etapa f*



Sal HCl

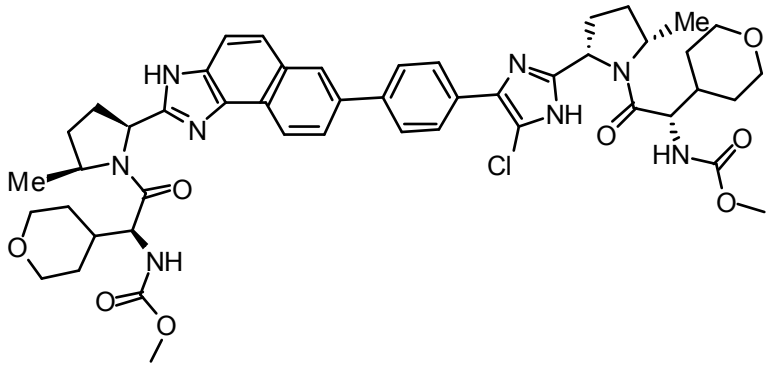
El Ejemplo JLR-4, etapa f, se preparó a partir del Ejemplo JLR-4, etapa e de acuerdo con el procedimiento descrito para la preparación del Ejemplo JLR-1, etapa b, dando el Ejemplo JLR-4, etapa f. CL/EM (Cond. J4): Tr = 2.19 min. CL/EM Anal. Calculado para $[M+H]^+$ $C_{30}H_{32}ClN_6$: 511.24; encontrado 711.23.

Ejemplo *JLR-4*

El Ejemplo JLR-4 se preparó a partir del Ejemplo JLR-4, etapa f, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2. La purificación se realizó mediante HPLC preparativa en columna Luna Axia (30 x 100 mm C 18) con un gradiente de 25 min de 15-100% de B a 40 ml/min), en la que el disolvente B = MeOH al 90%- H_2O al 10% – TFA al 0.1% y A = MeOH al 5% - H_2O al 95% - TFA al 0.1%. EM/CL (Cond. J4): Tr = 3.12 min. CL/EM Anal. Calculado

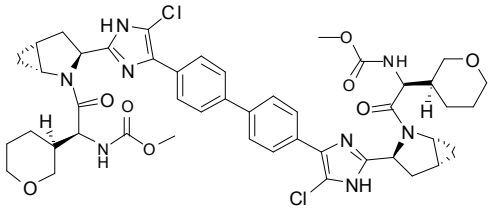
para $[M+H]^+$ $C_{44}H_{54}ClN_8O_6$: 825.39; encontrado 825.31.

Ejemplo *JLR-5*

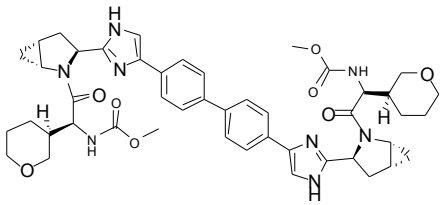


El Ejemplo JLR-5 se preparó a partir de la pirrolidina JLR-4, etapa f, de acuerdo con el procedimiento descrito para la preparación del Ejemplo GW2 a excepción de que se usó ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético . La purificación se realizó mediante HPLC preparativa en columna Luna Axia (30 x 100 mm C 18) con un gradiente de 25 min de 15-100% de B a 40 ml/min), en la que el disolvente B = MeOH al 90%- H_2O al 10% - TFA al 0.1% y A = MeOH al 5% - H_2O al 95% - TFA al 0.1%. EM/CL (Cond. J4): TR = 2.85 min. CL/EM Anal. calculado para $[M+H]^+$ $C_{48}H_{58}ClN_8O_6$: 909.41; encontrado 909.39.

Ejemplo *ZY1*



Ejemplo *ZY1, etapa a*



Se añadió HATU (151 mg, 0.40 mmol) a una solución de sal de HCl de 4.4'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)bifenilo (Ejemplo 1e) (107 mg, 0.18 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acético (cap-177a) (86 mg, 0.40 mmol) en DMF (1.5 ml) y DIPEA (0.25 ml, 1.4 mmol) y la mezcla se agitó a ta durante 2 h. La mezcla de reacción se diluyó con MeOH y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (S,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4,4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (148.5 mg) en foma de sólido amarillo claro. Tiempo de retención de CL-EM =1.61 min; m/z = 847 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.80 - 7.91 (m, 10 H), 5.13 (dd,

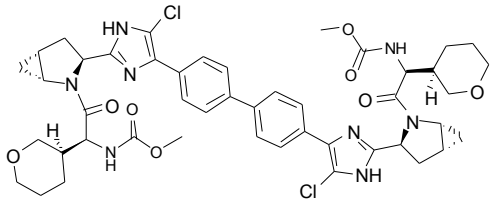
J=9.3, 7.0 Hz, 2 H), 4.79 (d, *J*=8.3 Hz, 2 H), 3.84 - 3.97 (m, 2 H), 3.70 - 3.80 (m, 4 H), 3.68 (s, 6 H), 3.52 – 3.63 (m, 2 H), 3.34 - 3.42 (m, 2 H), 2.61 – 2.75 (m, 2 H), 2.43 - 2.54 (m, 2 H), 1.98 - 2.15 (m, 4 H), 1.67 – 1.84 (m, 4 H), 1.48 - 1.65 (m, 4 H), 0.98 - 1.16 (m, 2 H), 0.77 - 0.93 (m, 2 H).

Ejemplo *ZY1*

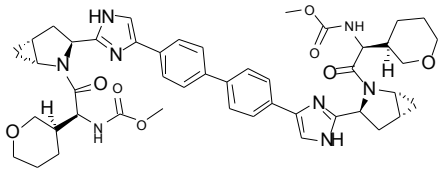
Se añadió NCS (8.2 mg, 0.061 mmol) a una solución de una sal de TFA de (S,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY1, etapa a) (33 mg, 0.031 mmol) en DMF (1 ml) y la mezcla se agito a 50°C durante 16 h. La mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (S,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(5-cloro-1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo, (Ejemplo ZY1) (25 mg) como sólido blanco. Tiempo de retención de CL-EM = 1.92 min; m/z = 458 $[M/2+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 95%/Metanol al 5%/Acetato de Amonio 10 mM. Disolvente B = Agua al 5%/Metanol al 95%/Acetato de Amonio 10 mM. Caudal = 4 ml/min. % inicial de B = 0. % final

de B = 100. Tiempo de gradiente = 2 min. Longitud de Onda = 220). RMN de ^{1}H (400 MHz, *MeOD*) δ ppm 7.77 - 7.85 (m, 8 H), 5.03 (dd, *J*=8.8, 6.0 Hz, 2 H), 4.75 – 4.86 (m, 2 H), 3.71 - 3.89 (m, 6 H), 3.67 (s, 6 H), 3.36 - 3.62 (m, 4 H), 2.38 - 2.57 (m, 4 H), 1.94 - 2.12 (m, 4 H), 1.69 - 1.87 (m, 4 H), 1.46 - 1.65 (m, 4 H), 1.03 - 1.17 (m, 2 H), 0.77 - 0.85 (m, 2 H).

Ejemplo *ZY2*



Ejemplo *ZY2, etapa a*



Se añadió HATU (140 mg, 0.37 mmol) a una solución de una sal de HCl de 4.4'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)bifenilo, (Ejemplo 1e) (100 mg, 0.17 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acético (cap117b) (80 mg, 0.37 mmol) en DMF (1.5 ml) y DIPEA (0.23 ml, 1.3 mmol) y la mezcla se agitó a ta durante 3 h. Después la mezcla de reacción se diluyó con MeOH y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (R,1S,1'S)-2,2'-

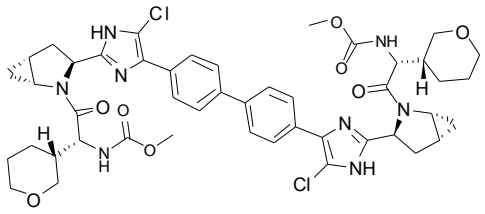
((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY2, etapa a) (76.2 mg) en forma de sólido blanco. Tiempo de retención CL-EM = 1.53 min; m/z = 847 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^{1}H (400 MHz, MeOD) δ ppm 7.75 - 7.96 (m, 10 H), 5.13 (dd, *J*=9.3, 7.0 Hz, 2 H), 4.60 (d, *J*=8.3 Hz, 2 H), 3.77 - 3.95 (m, 6 H), 3.67 (s, 6 H), 3.24 - 3.47 (m, 4 H), 2.62 - 2.76 (m, 2 H), 2.40 - 2.57 (m, 2 H), 1.97 - 2.19 (m, 4 H), 1.54 - 1.82 (m, 6 H), 1.36 - 1.54 (m, 2 H), 1.00 - 1.17 (m, 2 H), 0.79 - 0.93 (m, 2 H).

Ejemplo *ZY2*

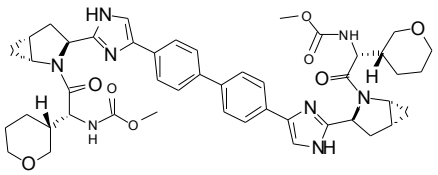
Se añadió NCS (5.2 mg, 0.039 mmol) a una solución de sal de TFA de (R,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY2, etapa a) (21 mg, 0.020 mmol) en DMF (1 ml) y la mezcla se agitó a 50°C durante 16 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se

purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (R,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(5-cloro-1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY2) (10.8 mg) en forma de sólido blanco. Tiempo de retención de CL-EM = 1.92 min; m/z = 458 $[M/2 + H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 95%/Metanol al 5%/Acetato de Amonio 10 mM. Disolvente B = Agua al 5%/Metanol al 95%/Acetato de Amonio 10 mM. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 2 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.76 - 7.87 (m, 8 H), 5.04 (dd, *J*=8.8, 6.0 Hz, 2 H), 4.61 (d, *J*=8.3 Hz, 2 H), 3.75 - 3.95 (m, 6 H), 3.66 (s, 6 H), 3.35 - 3.48 (m, 4 H), 2.39 - 2.58 (m, 4 H), 1.97 - 2.16 (m, 4 H), 1.73 - 1.87 (m, 2 H), 1.40 - 1.73 (m, 6 H), 1.01 - 1.16 (m, 2 H), 0.81 (d, *J*=1.8 Hz, 2 H).

Ejemplo *ZY3*



Ejemplo *ZY3, etapa a*



Se añadió HATU (82 mg, 0.22 mmol) a una solución de

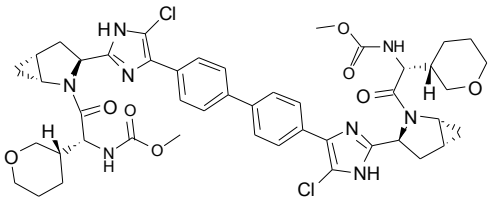
sal de HCl de 4.4'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)bifenilo (Ejemplo 1e) (58.3 mg, 0.098 mmol) y ácido (R)-2-(metoxicarbonilamino)-2-((R)-tetrahidro-2H-piran-3-il)acético (cap 117c) (49 mg, 0.23 mmol) en DMF (1 ml) y DIPEA (0.14 ml, 0.79 mmol) y la mezcla se agitó a ta durante 3 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (R,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY3, etapa a) (79.8 mg) como un sólido blanco. Tiempo de retención de CL-EM = 1.63 min; m/z = 847 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Velocidad de Flujo = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220).

Ejemplo *ZY3*

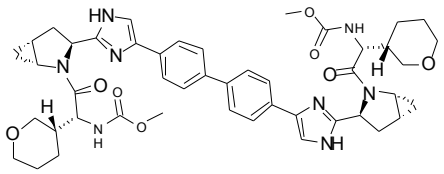
Se añadió NCS (6.7 mg, 0.050 mmol) a una solución de una sal de TFA de (R,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-

((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY3, etapa a) (27 mg, 0.025 mmol) en DMF (1 ml) y la mezcla se agitó a 50°C durante 16 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (R,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(5-cloro-1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY3) (15.8 mg) en forma de sólido blanco. Tiempo de retención de CL-EM = 1.93 min; m/z = 458 $[M/2 + H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 95%/Metanol al 5%/Acetato de Amonio 10 mM. Disolvente B = Agua al 5%/Metanol al 95%/Acetato de Amonio 10 mM. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 2 min. Longitud de onda = 220).

Ejemplo *ZY4*



Ejemplo *ZY4, etapa a*



Se añadió HATU (75 mg, 0.20 mmol a una solución de

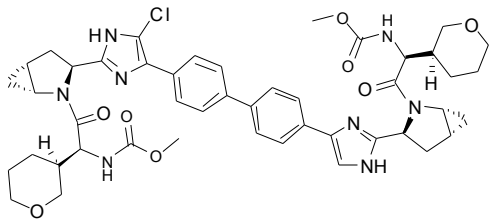
una sal de HCl de 4.4'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)bifenilo (Ejemplo 1e) (53.5 mg, 0.090 mmol) y ácido (R)-2-(metoxicarbonilamino)-2-((S)-tetrahidro-2H-piran-3-il)acético (cap117d) (45 mg, 0.21 mmol) en DMF (1 ml) y DIPEA (0.13 ml, 0.72 mmol) y la mezcla de agitó a ta durante 3 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (S,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY4, etapa a) (78.5 mg) en forma de sólido blanco. Tiempo de retención de CL-EM = 1.57 min; m/z = 847 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220).

Ejemplo *ZY4*

Se añadió NCS (9.2 mg, 0.069 mmol) a una solución de una sal de TFA de (S,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de

dimetilo (Ejemplo ZY4, etapa a) (37 mg, 0.034 mmol) en DMF (1 ml) y la mezcla se agitó a 50°C durante 16 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (S,1R,1'R)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(5-cloro-1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((S)-tetrahidro-2H-piran-3-yl)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY4) (25 mg) en forma de un sólido blanco. Tiempo de retención de CL-EM = 1.93 min; m/z = 458 $[M/2 + H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 95%/Metanol al 5%/Acetato de Amonio 10 mM. Disolvente B = Agua al 5%/Metanol al 95%/Acetato de Amonio 10 mM. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 2 min. Longitud de onda = 220).

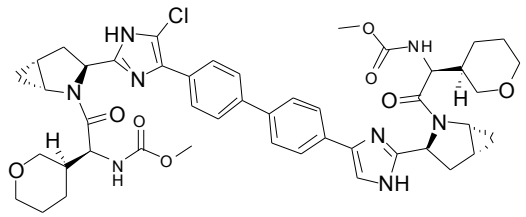
Ejemplo *ZY5*



Se añadió NCS (5.3 mg, 0.039 mmol) a una solución de una sal de TFA de (S,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-

((S)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY1, etapa a) (42.4 mg, 0.039 mmol) en DMF (1 ml) y la mezcla se agitó a 50°C durante 16 h. Después la mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando Ejemplo ZY5 como una sal de TFA (11.7 mg, sólido blanco). Tiempo de retención de CL-EM = 2.04 min; m/z = 881 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.76 - 7.92 (m, 9 H), 5.13 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.04 (dd, *J*=8.0, 6.5 Hz, 1 H), 4.74 - 4.80 (m, 2 H), 3.71 - 3.94 (m, 6 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.36 - 3.63 (m, 4 H), 2.63 - 2.75 (m, 1 H), 2.40 - 2.55 (m, 3 H), 1.95 - 2.15 (m, 4 H), 1.67 - 1.86 (m, 4 H), 1.45 - 1.65 (m, 4 H), 1.03 - 1.18 (m, 2 H), 0.84 - 0.91 (m, 1 H), 0.75 - 0.83 (m, 1 H).

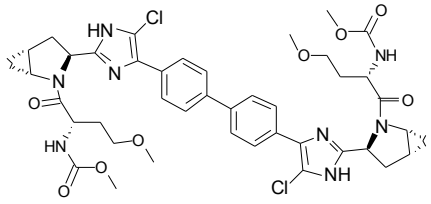
Ejemplo *ZY6*



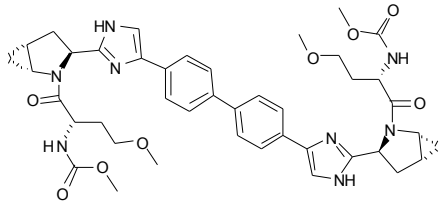
Se añadió NCS (1.1 mg, 8.4 µmol) a una solución de una

sal de TFA de (R,1S,1'S)-2,2'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(2-oxo-1-((R)-tetrahidro-2H-piran-3-il)etano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY2, etapa a) (8.1 mg, 8.4 µmol) en DMF (1 ml) y la mezcla se agitó a 50°C durante 16 h. Después la reacción se diluyó con MeOH, se filtro y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de Ejemplo ZY6 (2.2 mg) como un sólido blanco. Tiempo de retención de CL-EM = 2.01 min; m/z = 881 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.77 - 7.90 (m, 9 H), 5.12 (dd, *J*=9.2, 6.9 Hz, 1 H), 5.05 (dd, *J*=7.9, 6.1 Hz, 1 H), 4.58 - 4.96 (m, 2 H), 3.71 - 3.94 (m, 6 H), 3.68 (s, 3 H), 3.66 (s ancho,, 3 H), 3.34 - 3.46 (m, 4 H), 2.64 - 2.75 (m, 1 H), 2.40 - 2.54 (m, 3 H), 1.96 - 2.16 (m, 4 H), 1.40 - 1.85 (m, 8 H), 1.04 - 1.18 (m, 2 H), 0.84 - 0.92 (m, 1 H), 0.79 (m, 1 H).

Ejemplo *ZY7*



Ejemplo *ZY7, etapa a*



Se añadió HATU (95 mg, 0.25 mmol) a una solución de una sal de HCl de 4.4'-bis(2-((1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3-il)-1H-imidazol-4-il)bifenilo (Ejemplo 1e) (67.6 mg, 0.114 mmol) y ácido (S)-4-metoxi-2-(metoxicarbonilamino)butanoico (Ejemplo ZY7, etapa a) (50 mg, 0.26 mmol) en DMF (1 ml) y DIPEA (0.16 ml, 0.91 mmol) y la mezcla se agitó a ta durante 3 h. La mezcla de reacción se diluyó con MeOH, se filtró y se purificó por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (2S,2'S)-1,1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(4-metoxi-1-oxobutano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY7, etapa a) (96.4 mg) en forma de sólido blanco. Tiempo de retención de CL-EM = 1.53 min; m/z 795 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.78 - 7.97 (m, 10 H), 5.16 (dd, *J*=9.2, 6.7 Hz, 2 H), 4.76 - 4.83 (m, 2 H), 3.75 - 3.84

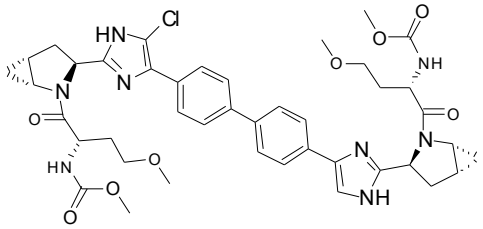
(m, 2 H), 3.66 (s, 6 H), 3.45 - 3.56 (m, 4 H), 3.32 (s, 6 H), 2.68 (dd, *J*=13.4, 9.4 Hz, 2 H), 2.42 - 2.53 (m, 2 H), 2.01 - 2.23 (m, 4 H), 1.80 - 1.95 (m, 2 H), 1.05 - 1.18 (m, 2 H), 0.78 – 0.98 (m, 2 H).

Ejemplo *ZY7*

Se añadió NCS (9.7 mg, 0.073 mmol) a una solución de una sal de TFA de (2S,2'S)-1,1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(4-metoxi-1-oxobutano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY7, etapa a) (29 mg, 0.036 mmol) en DMF (1 ml) y la mezcla se agito a 50°C durante 16 h. La mezcla de reacción se diluyó con MeOH, se filtro y se purifico por HPLC prep. (H_2O-MeOH con regulador de pH de TFA al 0.1%) proporcionando una sal de TFA de (2S,2'S)-1,1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(5-cloro-1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(4-metoxi-1-oxobutano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY7) (7.9 mg) en forma de sólido blanco. Tiempo de retención CL-EM = 2.51 min; m/z = 863 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. % final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^1H (400 MHz, *MeOD*) δ ppm 7.82 (s, 8 H), 5.07 (dd, *J*=8.5, 5.8

Hz, 2 H), 4.75 - 4.83 (m, 2 H), 3.70 - 3.76 (m, 2 H), 3.66 (s, 6 H), 3.44 - 3.54 (m, 4 H), 3.32 (s, 6 H), 2.39 - 2.57 (m, 4 H), 1.98 - 2.21 (m, 4 H), 1.82 - 1.94 (m, 2 H), 1.05 - 1.19 (m, 2 H), 0.78 - 0.92 (m, 2 H).

Ejemplo *ZY8*



Se añadió NCS (5.6 mg, 0.042 mmol) a una solución de na sal de TFA de (2S,2'S)-1,1'-((1R,1'R,3S,3'S,5R,5'R)-3,3'-(4.4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))bis(2-azabiciclo[3.1.0]hexano-3,2-diil))bis(4-metoxi-1-oxobutano-2,1-diil)dicarbamato de dimetilo (Ejemplo ZY7, etapa b) (33.3 mg, 0.042 mmol) en DMF (1 ml) y la mezcla se agitó a 50°C durnate 16 horas. La mezcla de reacción se diluyó com MeOH, se filtro y se purifico por HPLC prep. (H_2O-MeOH com regulador de pH de TFA al 0.1%) proporcionando una sal de TFA del Ejemplo ZY8 (9.4 mg) em forma de sólido blanco. Tiempo de retención de CL-EM = 1.99 min; m/z = 829 $[M+H]^+$. (Columna: Phenomenex-Luna 3.0 x 50 mm S10. Disolvente A = Agua al 90%: Metanol al 10%: TFA al 0.1%. Disolvente B = Agua al 10%: Metanol al 90%: TFA al 0.1%. Caudal = 4 ml/min. % inicial de B = 0. %

final de B = 100. Tiempo de gradiente = 3 min. Longitud de onda = 220). RMN de ^{1}H (400 MHz, MeOD) δ ppm 7.77 - 7.91 (m, 9 H), 5.15 (dd, J=9.2, 6.7 Hz, 1 H), 5.07 (t, J=7.0 Hz, 1 H), 4.77 - 4.83 (m, 2 H), 3.76 - 3.83 (m, 1 H), 3.68 - 3.75 (m, 1 H), 3.66 (s, 6 H), 3.44 - 3.56 (m, 4 H), 3.33 (s, 6 H), 2.63 - 2.75 (m, 1 H), 2.41 - 2.56 (m, 3 H), 1.97 - 2.23 (m, 4 H), 1.80 - 1.95 (m, 2 H), 1.06 - 1.19 (m, 2 H), 0.87 - 0.96 (m, 1 H), 0.84 (m, 1 H).

ACTIVIDAD BIOLÓGICA

Se utilizó un ensayo VHC Replicon en la presente descripción, y se preparó, realizó y validó como se describe en la patente del solicitante PCT/US2006/022197 y en O'Boyle et. Al. Antimicrob Agents Chemother.; 49(4):1346-1353 (abril de 2005). También se han usado procedimientos de ensayo que incorporan informadores de luciferasa como se describe (Apath.com).

Se usaron células con el replicón VHC-neo y células con replicón que contenían sustituciones de resistencia en la región NS5A para ensayar la familia de compuestos descritos en este documento. Se determinó que los compuestos tenían diferentes grados de actividad inhibidora reducida en las células que contenían mutaciones frente a la potencia inhibidora

correspondiente contra las células de tipo silvestre. Por lo tanto, los compuestos de la presente descripción pueden ser eficaces para inhibir la función de la proteína NS5A del VHC y se entiende que son tan eficaces en combinaciones como se ha descrito anteriormente en la solicitud de patente PCT/US2006/022197 y en la patente del solicitante WO04/014852. Debe entenderse que los compuestos de la presente descripción pueden inhibir múltiples genotipos del VHC. La Tabla 2 muestra los valores de CE_{50} (Concentración eficaz inhibidora al 50 %) de compuestos representativos de la presente descripción contra el genotipo 1b del VHC. En una modalidad, los compuestos de la presente descripción son inhibidores de los genotipos 1a, 1b, 2a, 2b, 3a, 4a y 5a. Los valores de CE_{50} contra 1b del VHC son como sigue. Los valores de CE_{50} contra 1b del VHC son como sigue: A = 0.2 pM -<1 pM; B = 1 pM - <10 pM; y C = 10 pM -< 100 pM; y D = 100 pM-0.15 µM.

Los compuestos de la presente descripción pueden inhibir VHC mediante mecanismos además de, o distintos a, la inhibición de NS5A. En una modalidad, los compuestos de la presente descripción inhiben el replicón del VHC y en otra modalidad los compuestos de la presente descripción inhiben NS5A.

Tabla 2

Ejemplo	**CE_{50} (uM)**	**Intervalo CE_{50}-**
M1		B
M2		B
M4		B
M5		B
M6	4.08E-06	B
M7	2.13E-06	B
V1		B
V2	8.88E-05	C
V3		B
V4	3.22E-05	C
V5	6.58E-07	A
V5.1	3.90E-06	B
V5.2	3.06E-05	C
V5.3	1.33E-04	D
V6		A
V7		B
V8		B
V9	2.70E-06	B
V10		B
V11		B
V12		B

Ejemplo	**CE_{50} (uM)**	**Intervalo CE_{50}-**
V13		B
V14		B
V15		C
V16	9.66E-07	A
GW1-1		B
GW1-2		B
GW1-3		B
GW2		B
GW2-1	1.27E-05	C
GW3		B
GW4		C
GW5		B
GW6		B
GW7		B
GW8		B
GW9		A
GW10		B
GW11		A
GW12		A
OL1	3.06E-06	B
OL2		B
OL3		B

Ejemplo	**CE_{50} (uM)**	**Intervalo CE_{50}-**
OL4		B
OL5		B
OL6		B
OL7		B
OL8	2.09E-04	D
OL9	6.08E-06	B
OL10		D
OL11		B
OL12		C
OL13		B
OL14		C
OL15		B
OL16		C
OL17		B
OL18		B
OL19		C
OL20		D
OL21		C
OL22	4.08E-04	D
OL23		D
OL24		B
OL25		D

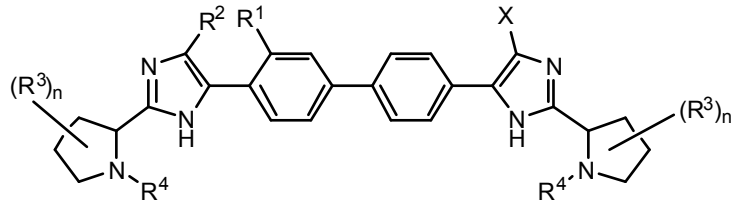
Ejemplo	**CE_{50} (uM)**	**Intervalo CE_{50}-**
DSTL-1		A
DSTL-2		C
DSTL-3	1.25E-06	B
DSTL-4		A
DSTL-5	5.59E-07	A
DSTL-6		B
DSTL-7		B
DSTL-8		A
DSTL-9		B
DSTL-10		B
DSTL-11		A
DSTL-12		C
DSTL-1		A
DSTL-2		C
DSTL-3	1.25E-06	B
DSTL-4		A
JLR-1		B
JLR-2		B
JLR-3		A
JLR-4	7.69E-07	A
JLR-5		B
ZY1		B

Ejemplo	**CE_{50} (uM)**	**Intervalo CE_{50}-**
ZY2		B
ZY3		B
ZY4		B
ZY5		B
ZY6	1.08E-05	C
ZY7		B
ZY8		B

Será evidente para un experto en la técnica que la presente descripción no se limita a los anteriores ejemplos ilustrativos, y que puede realizarse en otras formas específicas sin separarse de sus atributos esenciales. Por lo tanto se desea que los ejemplos sean considerados en todos los respectos como ilustrativos y como no restrictivos, haciendo referencia a las reivindicaciones anexas, en lugar de a los ejemplos anteriores, y por lo tanto se pretende que todos los cambios que entren dentro del significado y del alcance de equivalencia de las reivindicaciones estén incluidos en ellas.

REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I),

o una sal farmacéuticamente aceptable del mismo; caracterizados porque

n es 0, 1 ó 2;

X está seleccionado de entre hidrógeno, alquenilo, ciano, cicloalquilo, (cicloalquil)alquilo, halo y heterociclilo;

R^1 está seleccionado de entre hidrógeno y halo;

R^2 está seleccionado de entre hidrógeno, alquenilo, ciano, cicloalquilo, (cicloalquil)alquilo, halo y heterociclilo; o

R^1 y R^2, junto con los átomos de carbono a los que están unidos, forman un anillo aromático de seis miembros sustituidos opcionalmente con un grupo halo;

con la condición de que al menos uno de X y R^2 está seleccionado de entre alquenilo, ciano, cicloalquilo, (cicloalquilalquilo), halo y heterociclilo;

cada R^3 es alquilo, en el que el alquilo puede, opcionalmente, formar un anillo condensado de tres o cuatro miembros con un átomo de carbono

adyacente o un anillo espirocíclico de tres o cuatro miembros con el átomo de carbono al que está unido; en el que los anillos condensados y espirocíclicos están opcionalmente sustituidos con uno o dos grupos alquilo;

cada R^4 está seleccionado independientemente de hidrógeno y $-C(O)R^5$; y

cada R^5 está seleccionado independientemente de alcoxi, alquilo, arilalcoxi, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, (NR^cR^d)alquenilo y (NR^cR^d)alquilo.

2. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizados porque cada R^5 está seleccionado de forma independiente de alcoxi, heterociclilo y (NR^cR^d)alquilo.

3. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizados porque X es halo.

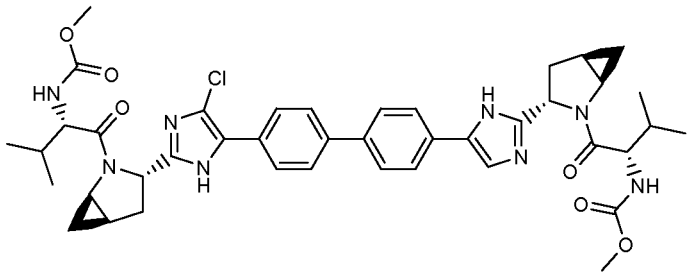
4. El compuesto de conformidad con la reivindicación 3, o una sal farmacéuticamente aceptable del mismo, caracterizados porque R^2 es halo.

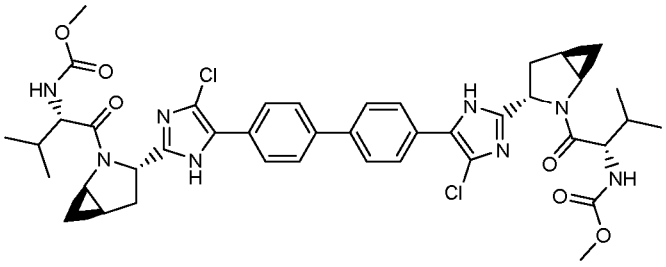
5. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizados porque R^1 y R^2,

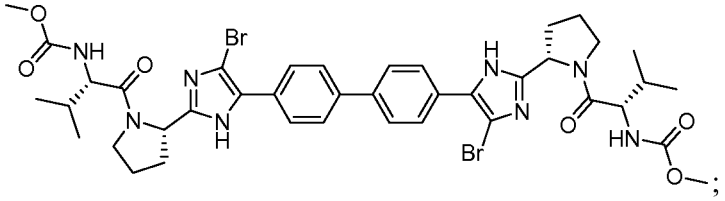
junto con los átomos de carbono a los que están unidos, forman un anillo aromático de seis miembros sustituidos opcionalmente con un grupo halo.

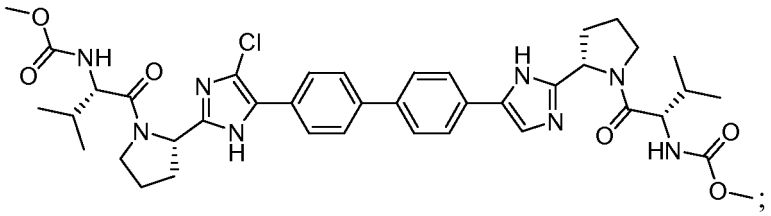
6. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizados porque X es hidrógeno.

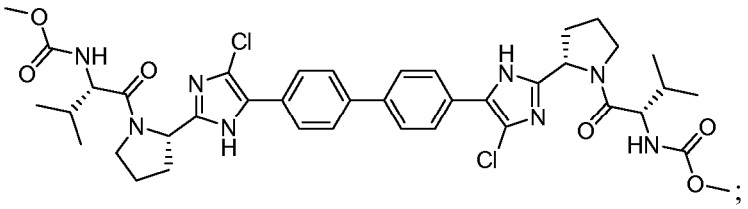
7. Un compuesto caracterizado porque se selecciona de:

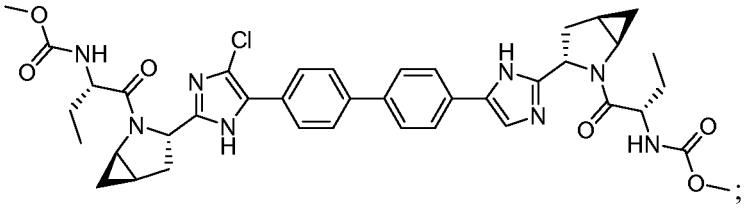

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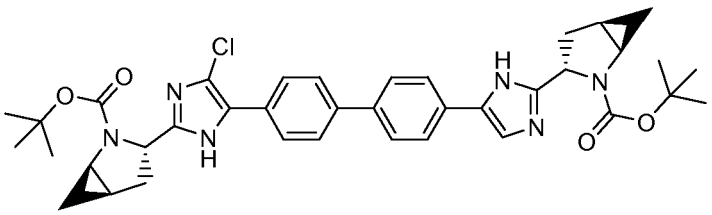

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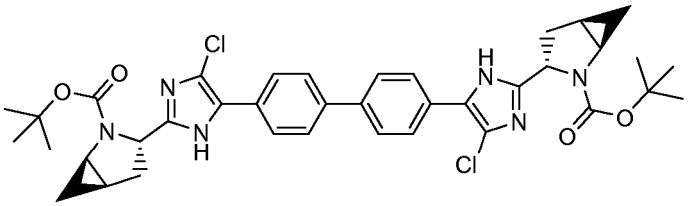




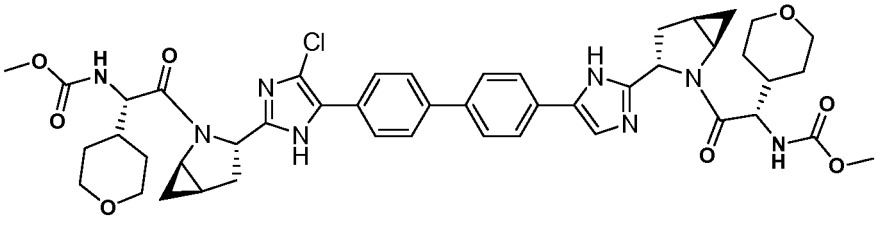




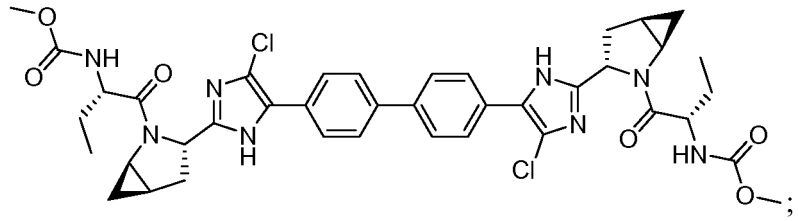
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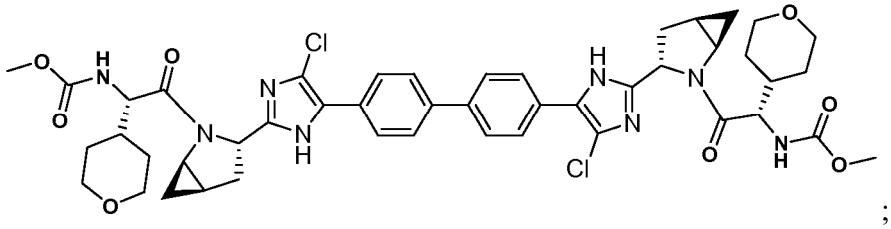


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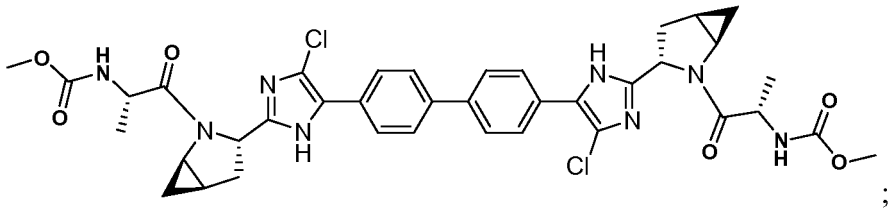


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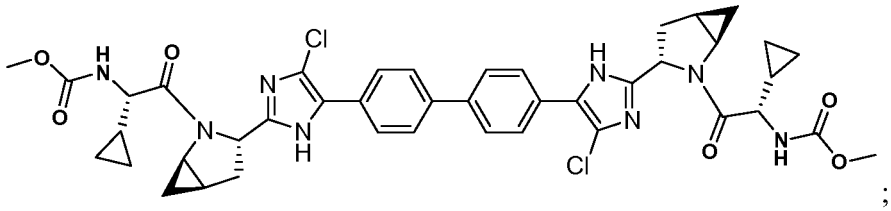




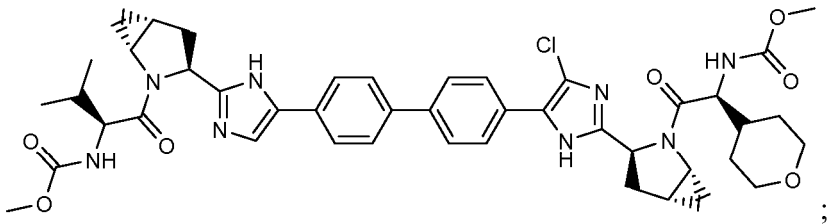
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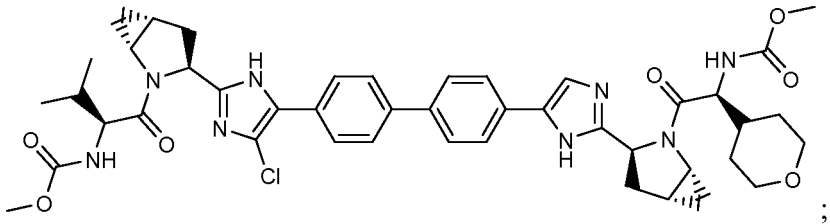
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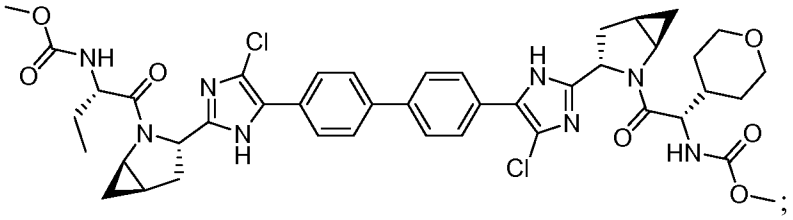
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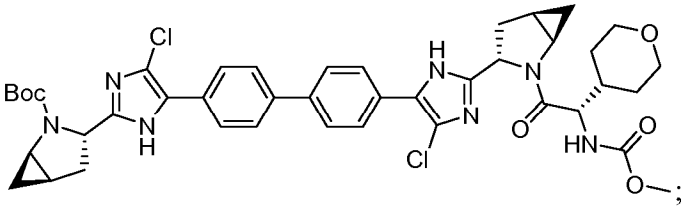


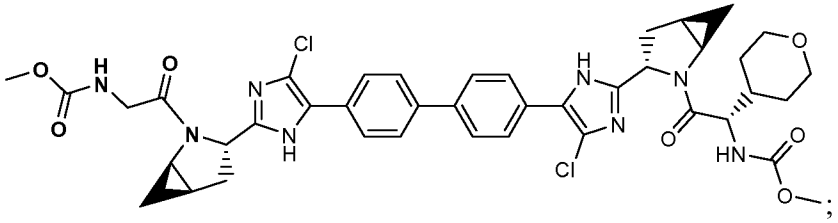
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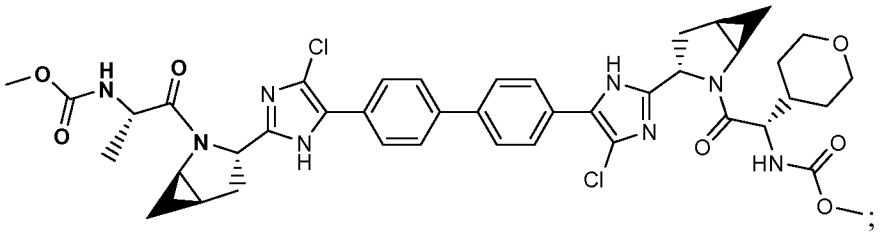


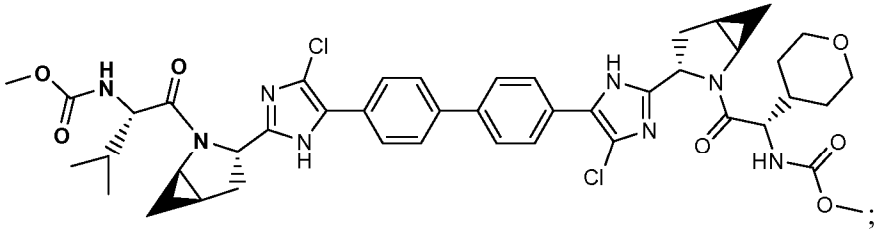
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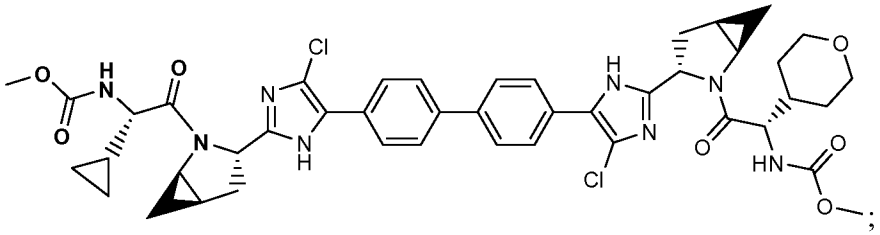


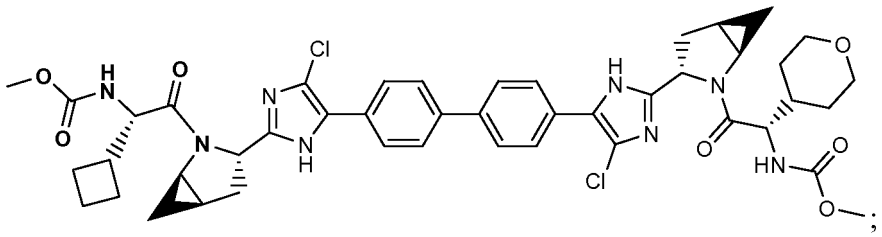


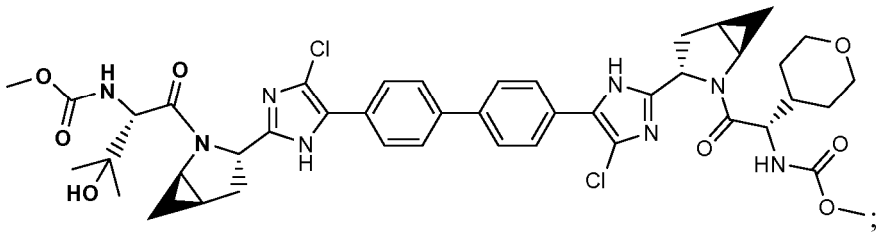


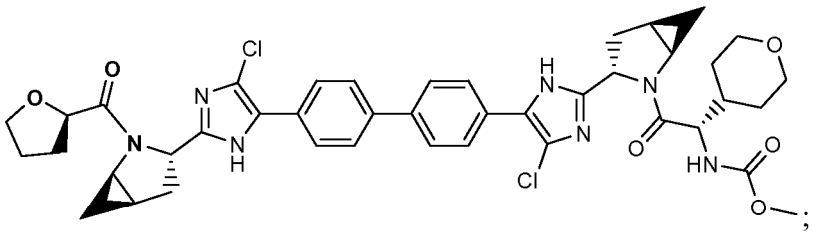


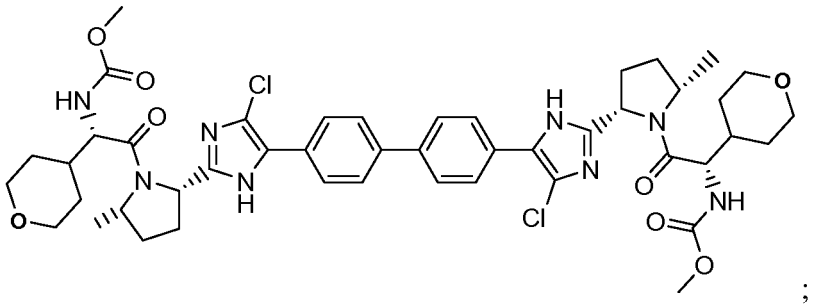




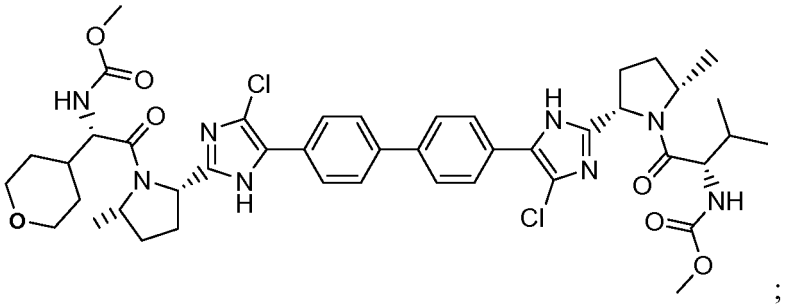




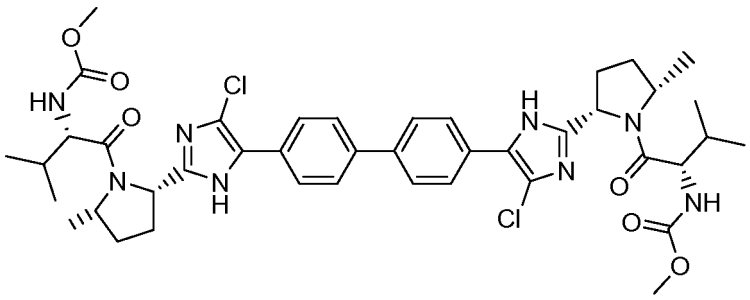


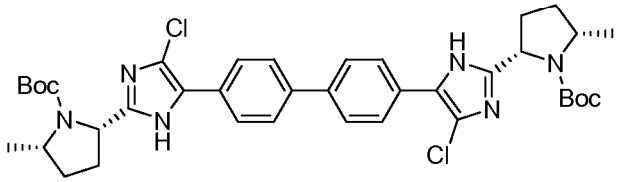


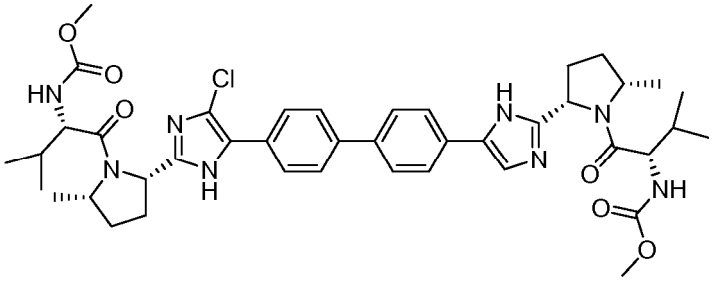
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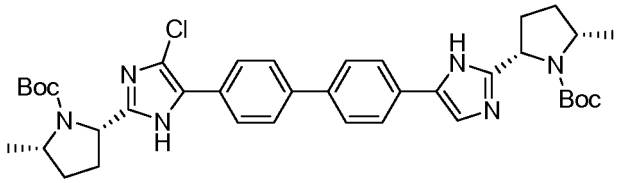


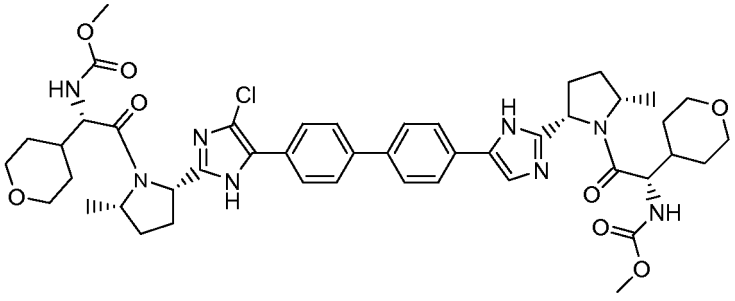
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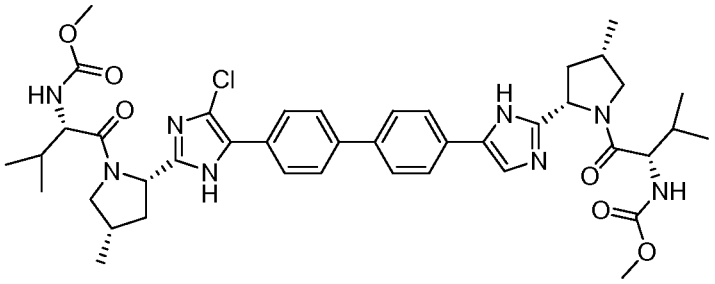

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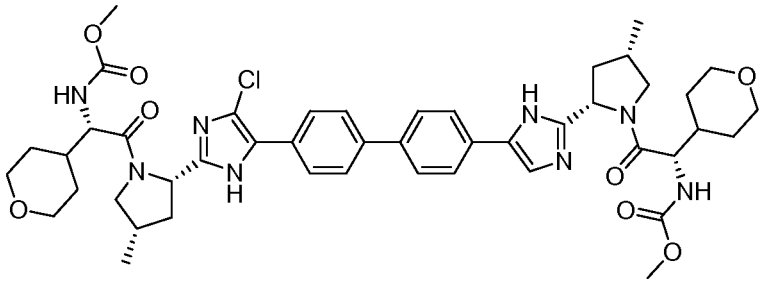

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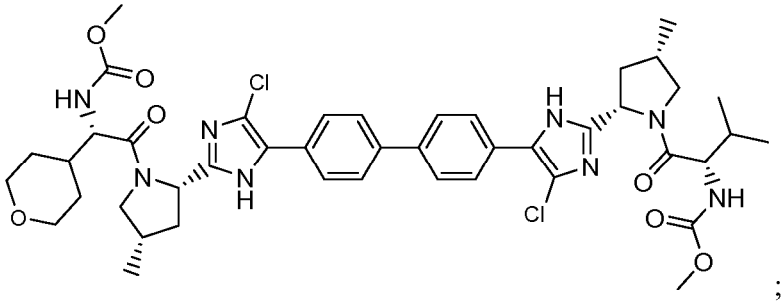

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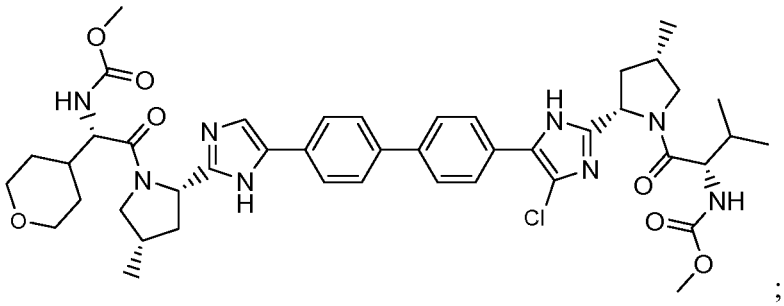

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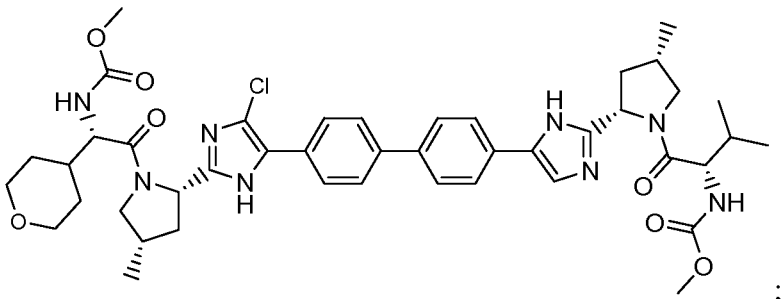

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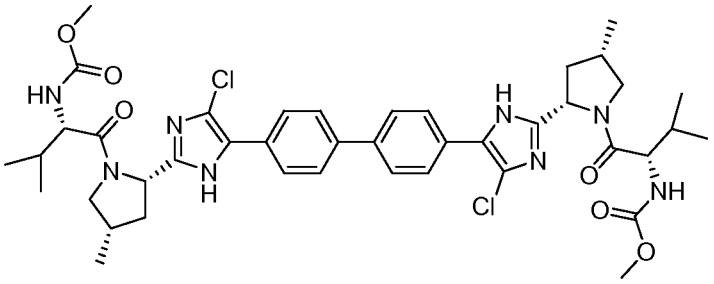

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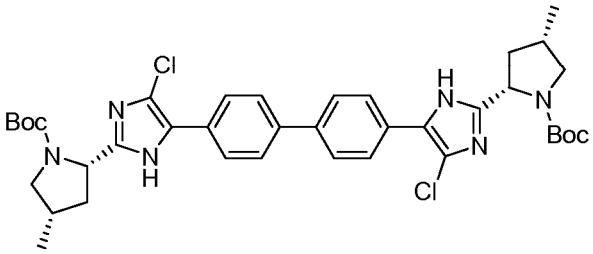

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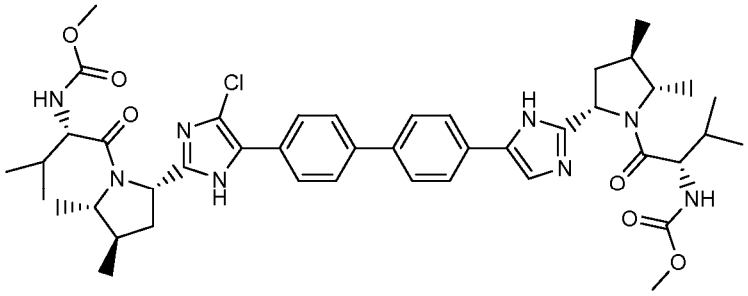

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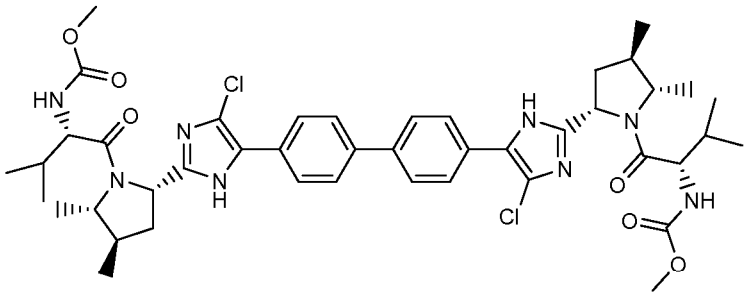

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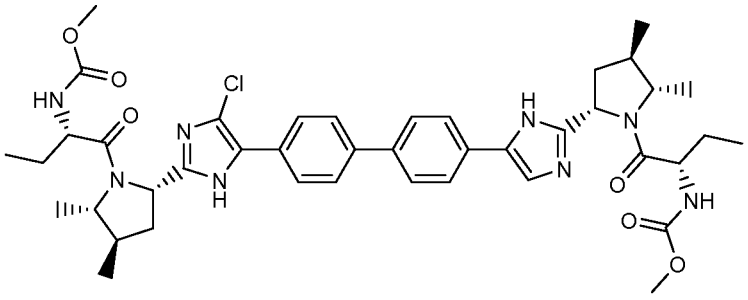

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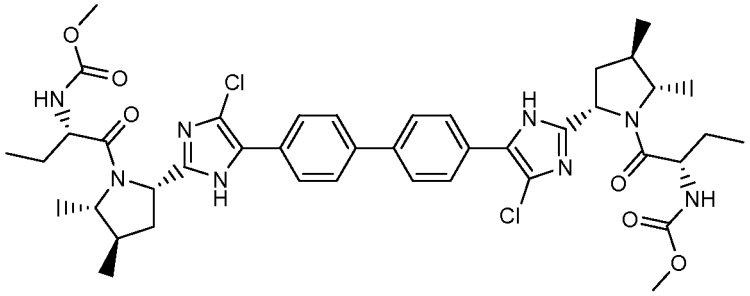

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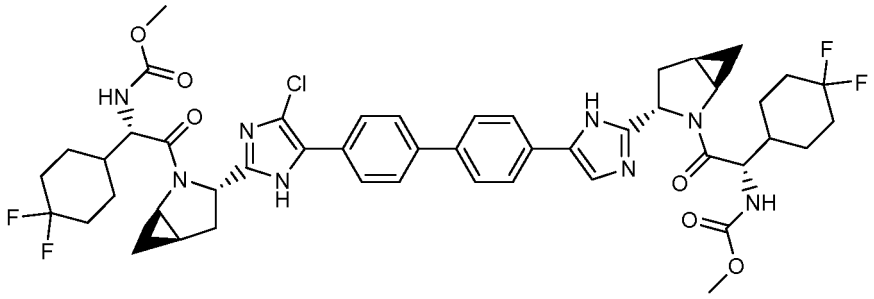

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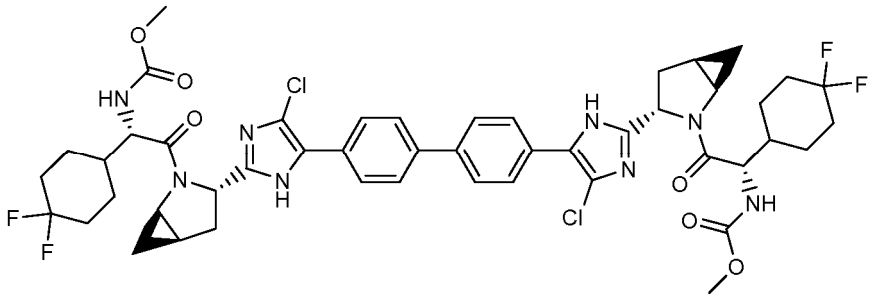

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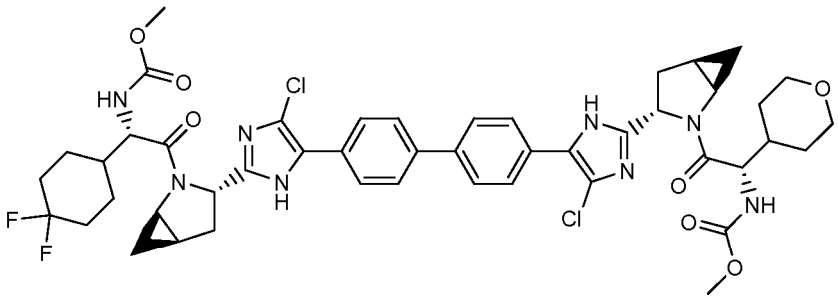

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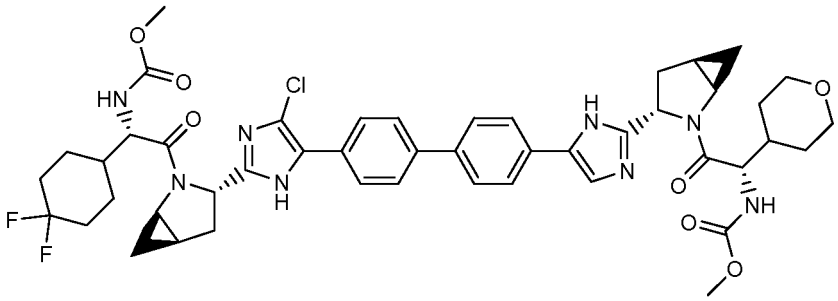

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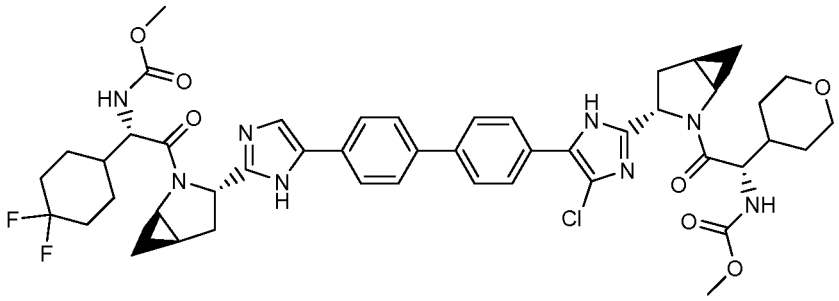

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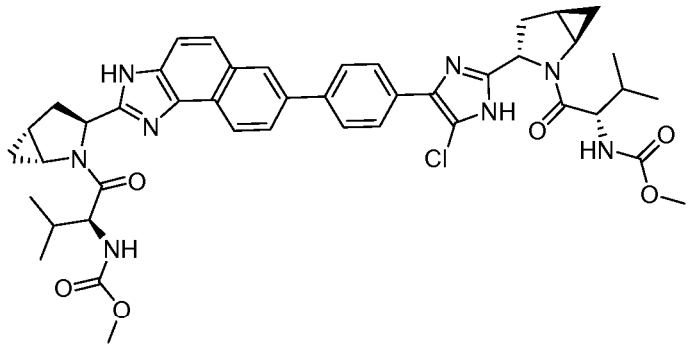

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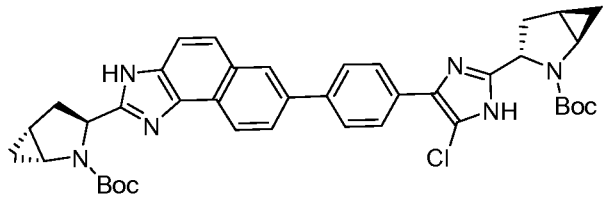

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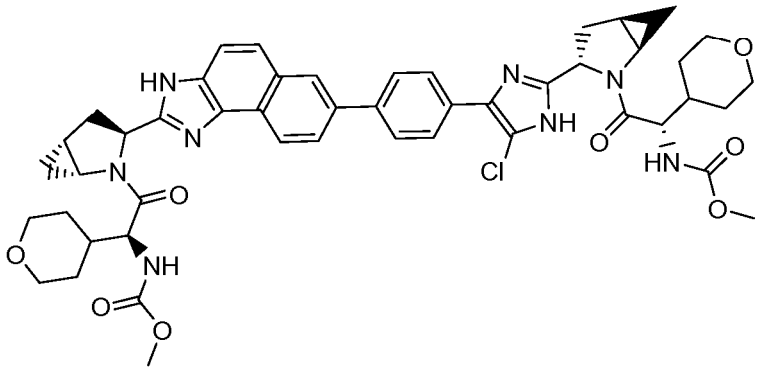
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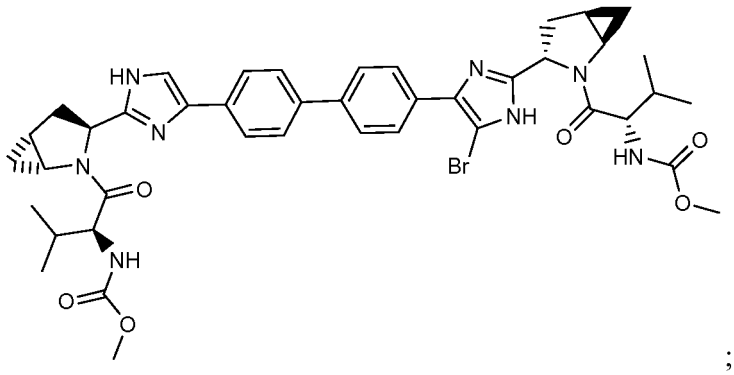
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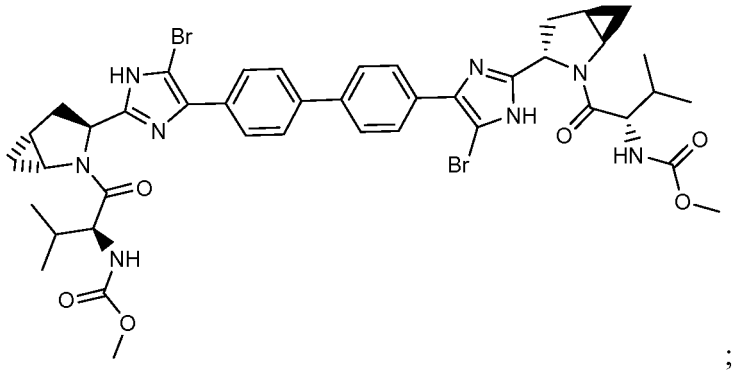
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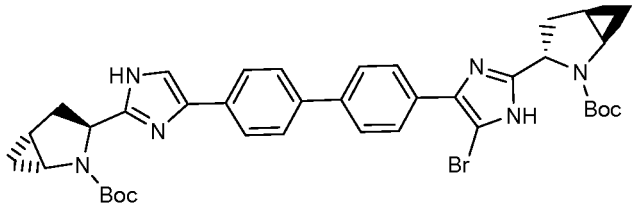
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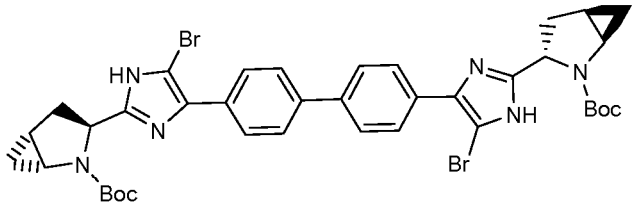
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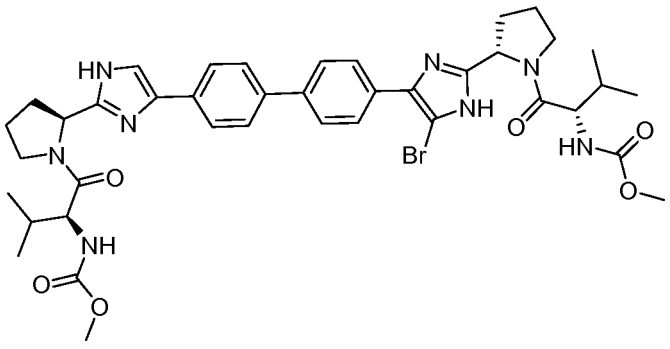
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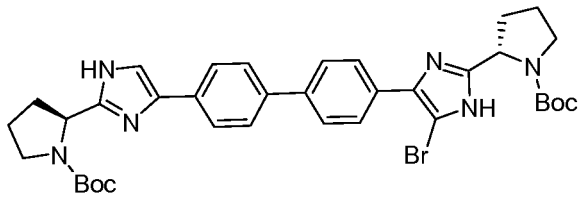
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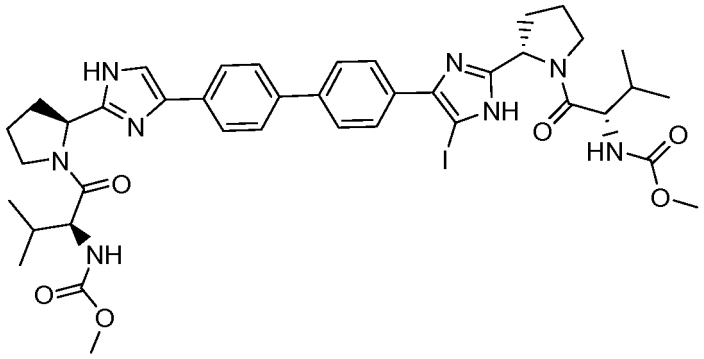
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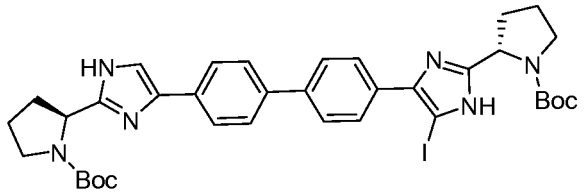
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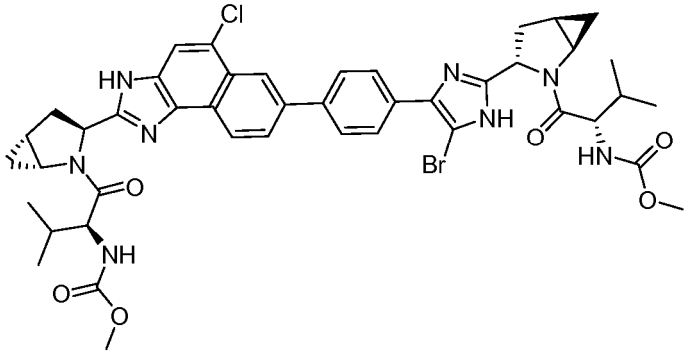
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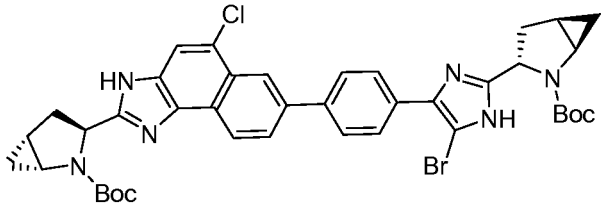
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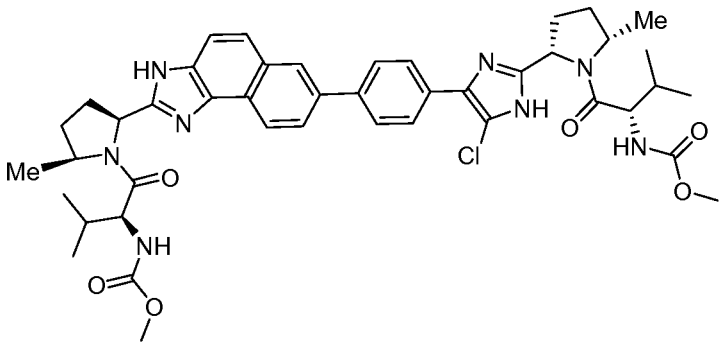
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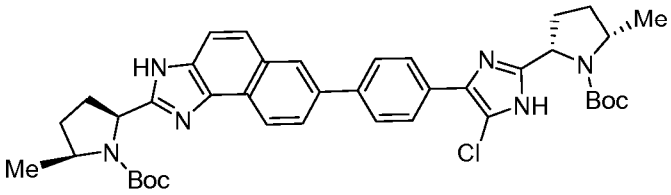
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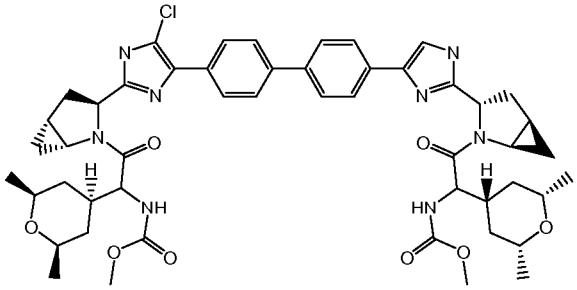
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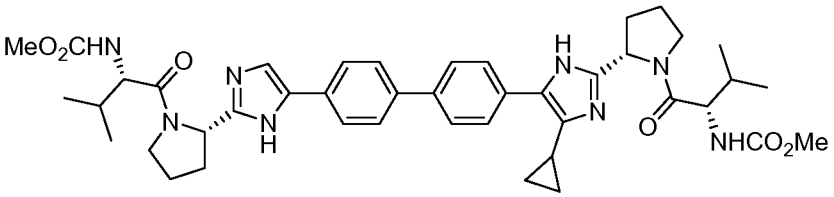
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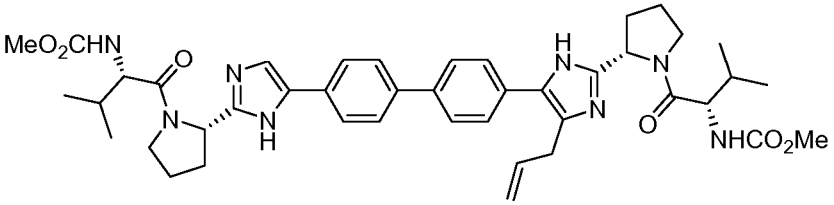
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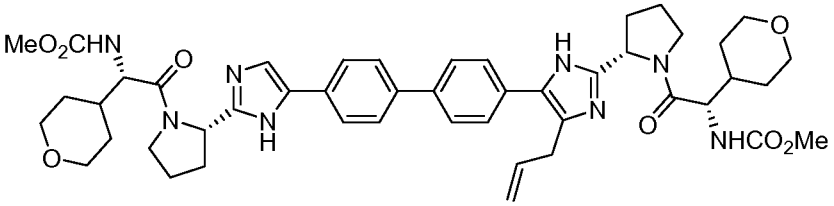
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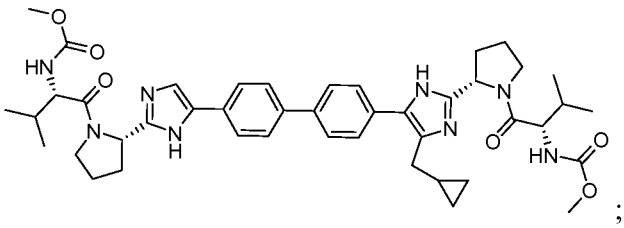
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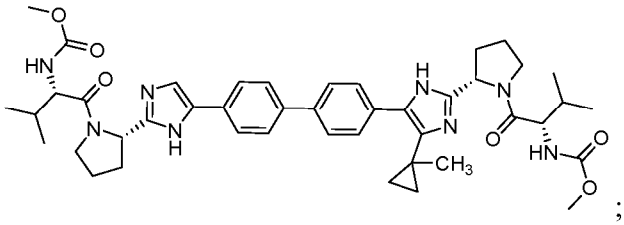


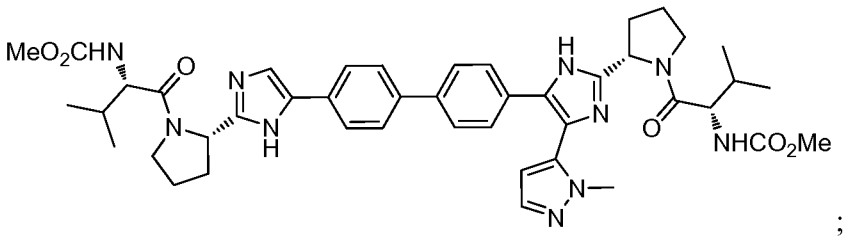
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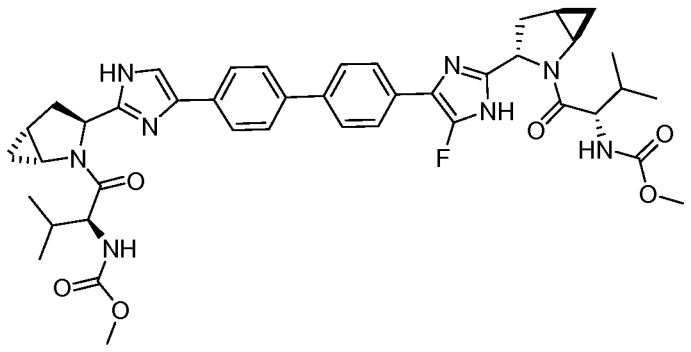


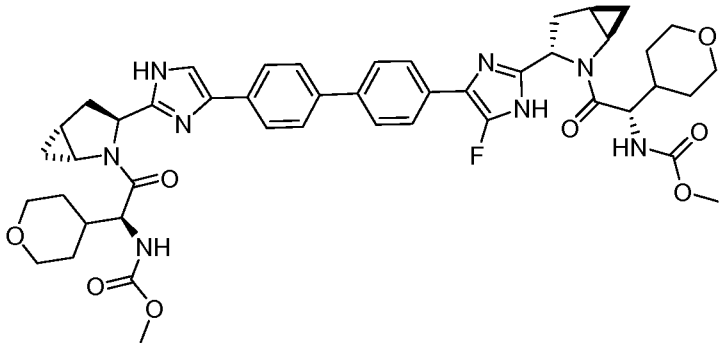
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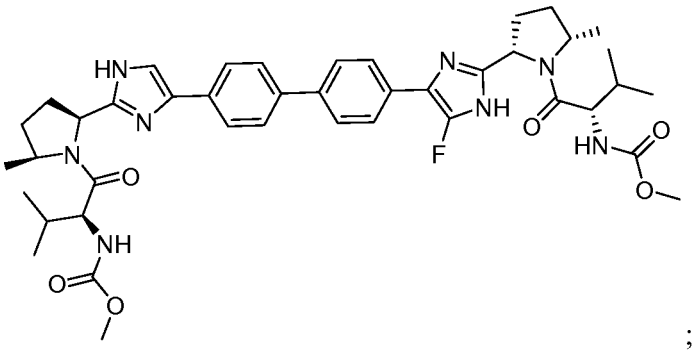

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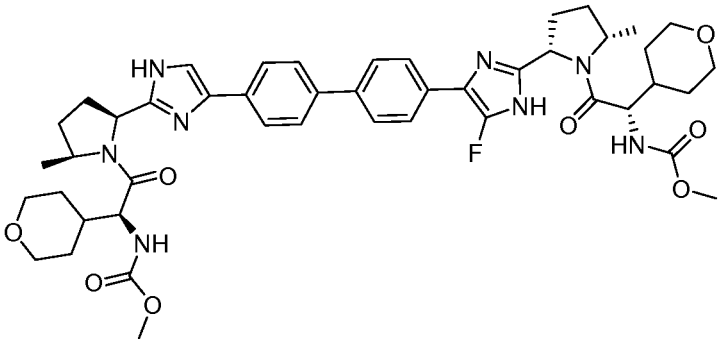

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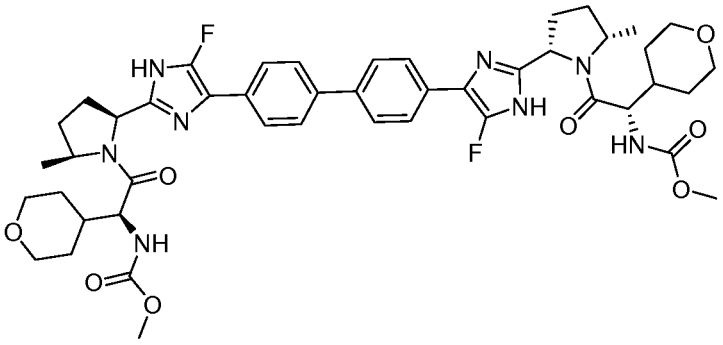

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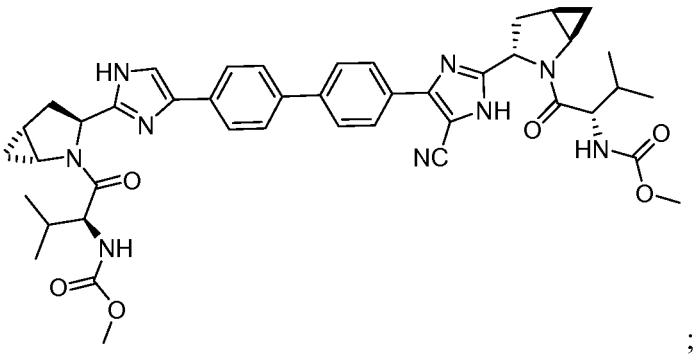
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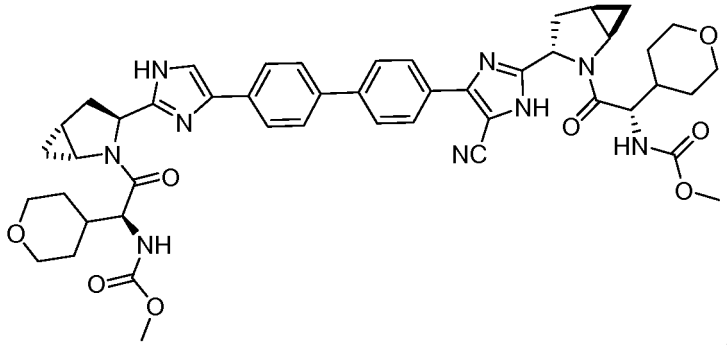
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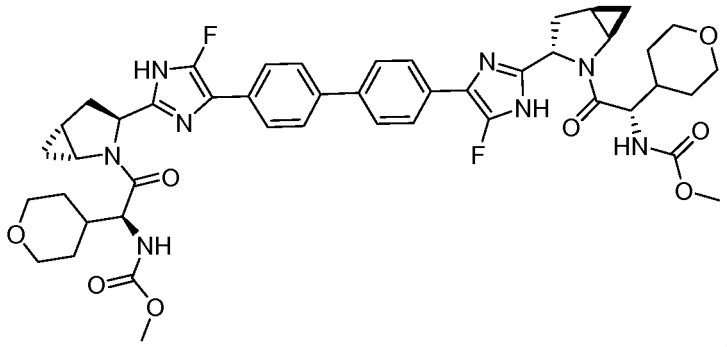
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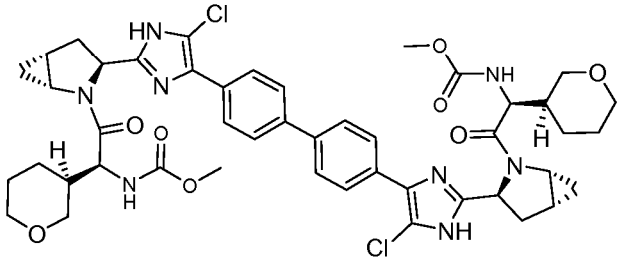
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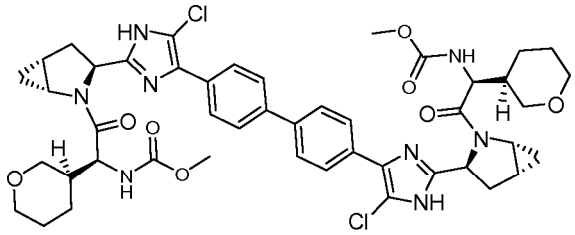
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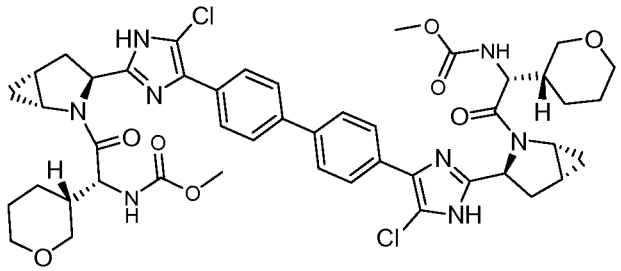
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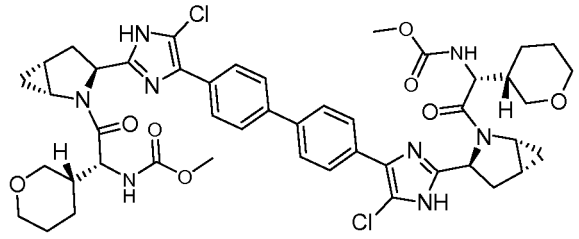
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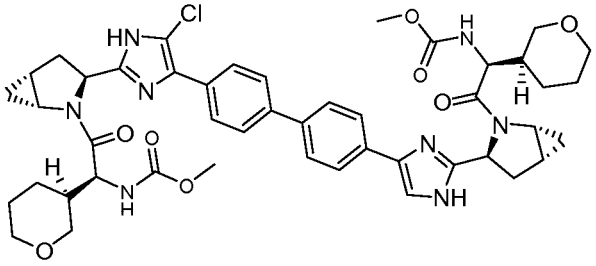


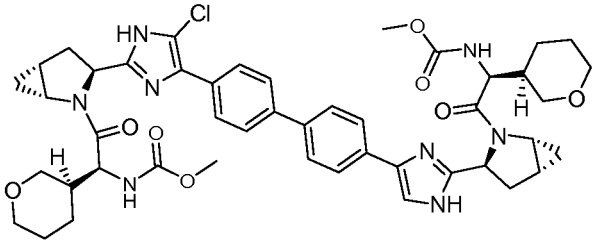
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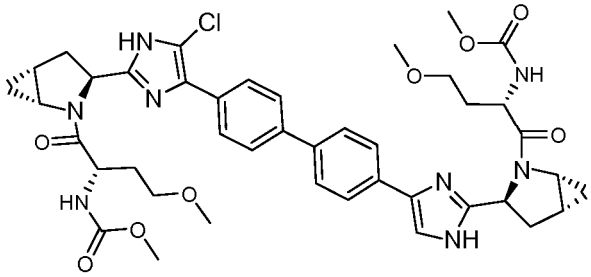


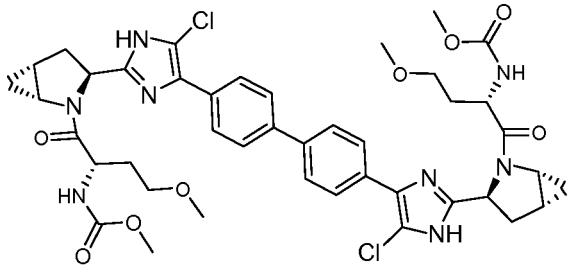
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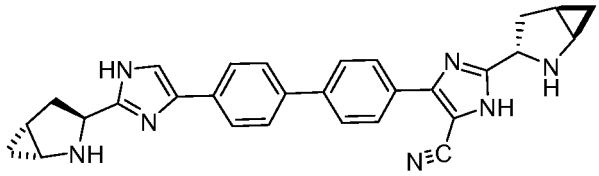

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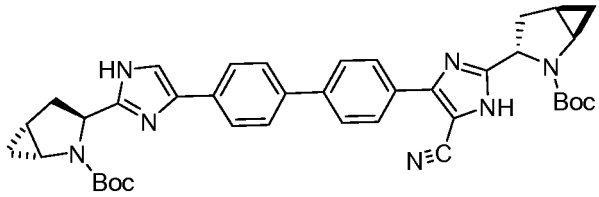

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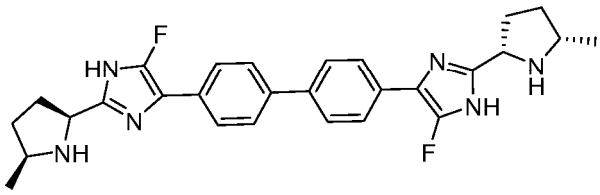

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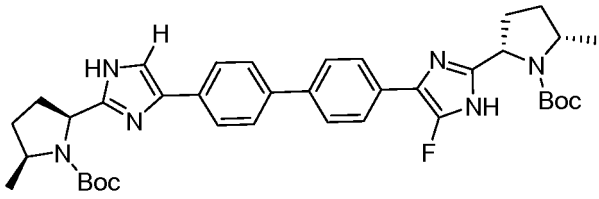

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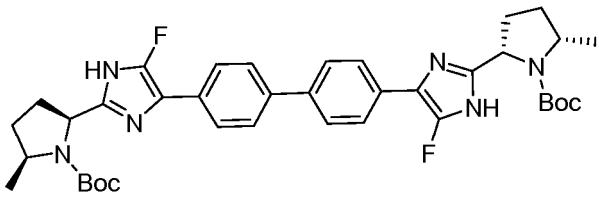

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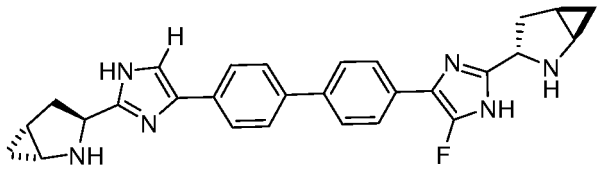

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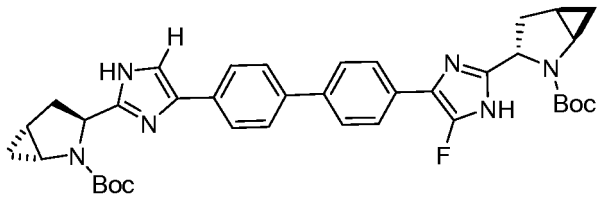

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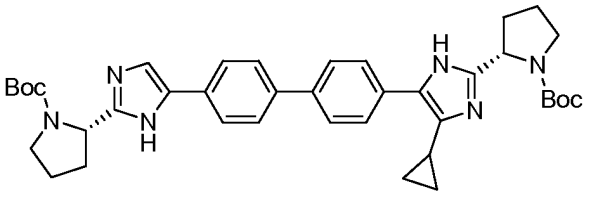

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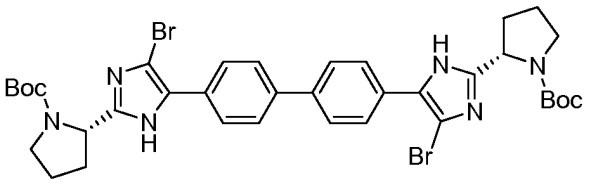

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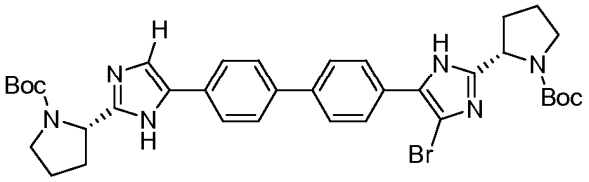

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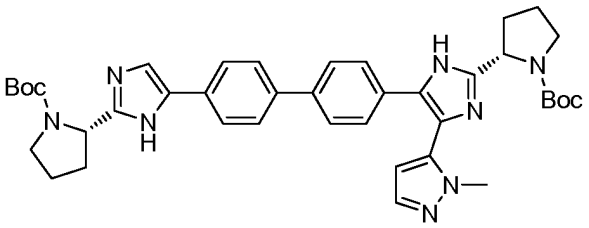

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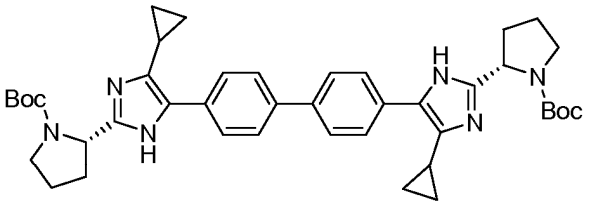

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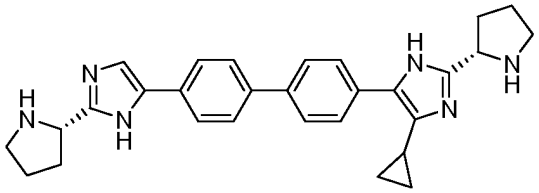

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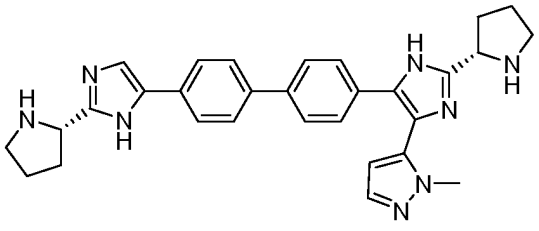

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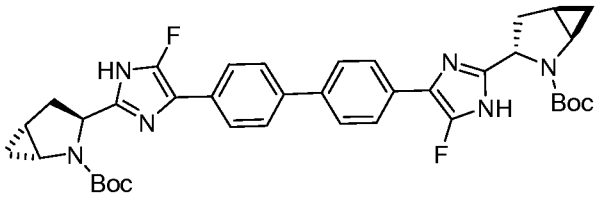

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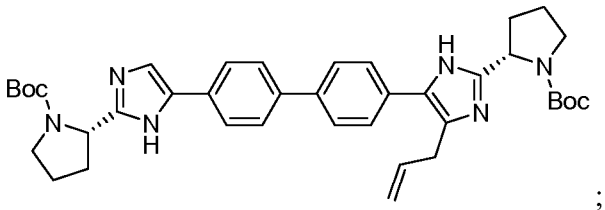

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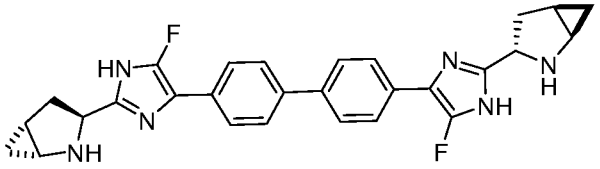

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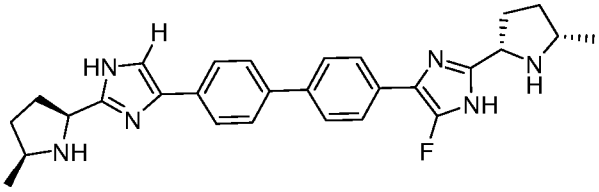
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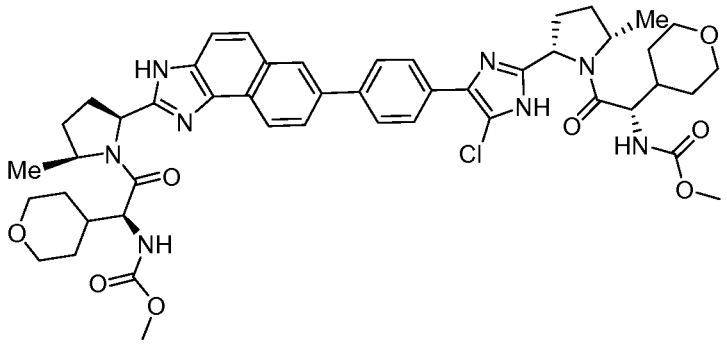
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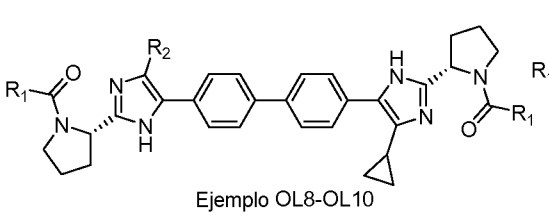
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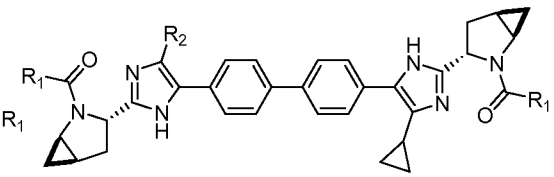
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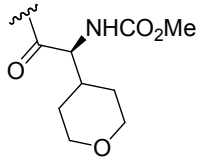
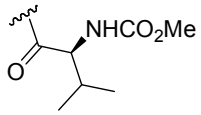
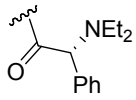
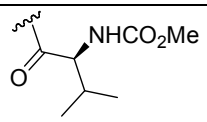
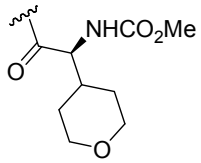
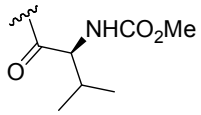
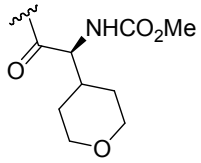
8. Un compuesto caracterizado porque se selecciona de



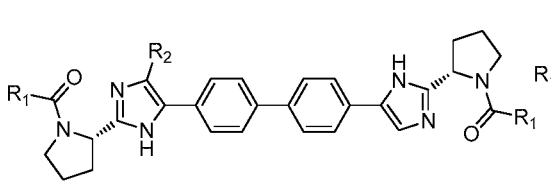
Ejemplo OL8-OL10



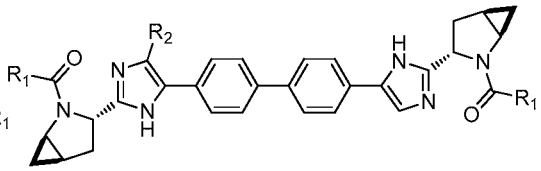
Ejemplo OL11-OL14

Ejemplo		R_2
OL8		H
OL9		
OL10		
OL11		H
OL12		H
OL13		
OL14		

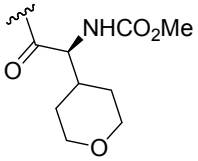
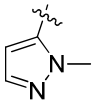
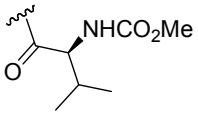
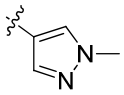
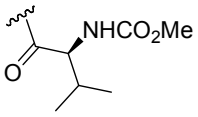
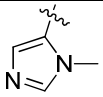
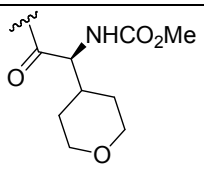
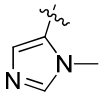
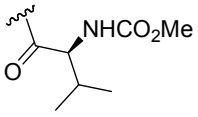
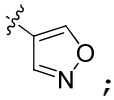
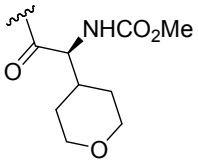
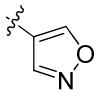
;



Ejemplo OL20-OL23



Ejemplo OL24-OL25

Ejemplo		R_2
OL20		
OL21		
OL22		
OL23		
OL24		 ; y
OL25		

; o una sal farmacéuticamente aceptable de los mismos.

9. Una composición caracterizada porque comprende el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

10. La composición de conformidad con la reivindicación 8, caracterizada porque además comprende al menos un compuesto adicional que tiene actividad contra el VHC.

11. La composición de conformidad con la reivindicación 9, caracterizada porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

12. La composición de conformidad con la reivindicación 11, caracterizada porque el interferón está seleccionado de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

13. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales está seleccionado de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de la respuesta de linfocitos T auxiliares de tipo 1, ARN de interferencia, ARN antisentido, imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amadantina y rimantadina.

14. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC y IMPDH para el tratamiento de una infección por el VHC.

15. Un método de tratamiento de una infección por

VHC en un paciente, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

16. El método de conformidad con la reivindicación 15, caracterizado porque además comprende administrar al menos uno de los compuestos adicionales que tiene actividad contra el VHC antes de, después de, o simultáneamente con, el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

17. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

18. El método de conformidad con la reivindicación 17, caracterizado porque el interferón está seleccionado de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A e interferón linfoblastoide tau.

19. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales está seleccionado de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de la respuesta de linfocitos T auxiliares de tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amadantina y rimantadina.

20. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana seleccionada de metaloproteasa del VHC, serina proteasa del VHC, polimerasa del VHC, helicasa del VHC, proteína NS4B del VHC, entrada del VHC, ensamblaje del VHC, salida del VHC, proteína NS5A del VHC y IMPDH para el tratamiento de una infección por el VHC.

RESUMEN DE LA INVENCION

La presente descripción se refiere a compuestos, composiciones y métodos para el tratamiento de infección por el virus de la hepatitis C (VHC). También se describen composiciones farmacéuticas que contienen los compuestos y métodos para usar los compuestos en el tratamiento de infección por VHC.

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

1

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

2

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

BAKER & MCKENZIE

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ
Estados Unidos de América
suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituída, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

5

PCT REQUEST

Original (for **SUBMISSION**)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from BELEMA, Makonen to BRISTOL-MYERS SQUIBB COMPANY, dated 05 January 2010 (05.01.2010)
VIII-2-1(iv)		an assignment from ROMINE, Jeffrey Lee to BRISTOL-MYERS SQUIBB COMPANY, dated 05 January 2010 (05.01.2010)
VIII-2-1(iv)		an assignment from NGUYEN, Van N. to BRISTOL-MYERS SQUIBB COMPANY, dated 04 January 2010 (04.01.2010)
VIII-2-1(iv)		an assignment from WANG, Gan to BRISTOL-MYERS SQUIBB COMPANY, dated 22 December 2009 (22.12.2009)
VIII-2-1(iv)		an assignment from LOPEZ, Omar D. to BRISTOL-MYERS SQUIBB COMPANY, dated 18 December 2009 (18.12.2009)
VIII-2-1(iv)		an assignment from ST. LAURENT, Denis R. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 December 2010 (01.12.2010)
VIII-2-1(iv)		an assignment from CHEN, Qi to BRISTOL-MYERS SQUIBB COMPANY, dated 01 December 2010 (01.12.2010)
VIII-2-1(iv)		an assignment from BENDER, John A. to BRISTOL-MYERS SQUIBB COMPANY, dated 01 December 2010 (01.12.2010)
VIII-2-1(iv)		an assignment from YANG, Zhong to BRISTOL-MYERS SQUIBB COMPANY, dated 02 December 2010 (02.12.2010)
VIII-2-1(iv)		an assignment from HEWAWASAM, Piyasena to BRISTOL-MYERS SQUIBB COMPANY, dated 02 December 2010 (02.12.2010)
VIII-2-1(iv)		an assignment from XU, Ningning to BRISTOL-MYERS SQUIBB COMPANY, dated 01 December 2010 (01.12.2010)
VIII-2-1(iv)		an assignment from MEANWELL, Nicholas A. to BRISTOL-MYERS SQUIBB COMPANY, dated 18 December 2009 (18.12.2009)

VIII-2-1(iv)		an assignment from EASTER, John A. to BRISTOL-MYERS SQUIBB COMPANY, dated 21 December 2009 (21.12.2009)
VIII-2-1(iv)		an assignment from SU, Bao-Ning to BRISTOL-MYERS SQUIBB COMPANY, dated 21 December 2009 (21.12.2009)
VIII-2-1(iv)		an assignment from SMITH, Michael J. to BRISTOL-MYERS SQUIBB COMPANY, dated 19 December 2009 (19.12.2009)

PATENT COOPERATION TREATY PCT/US2010/060077

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

MINGO, Pamela, A.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
01 June 2012 (01.06.2012)

Applicant's or agent's file reference
11543WOPCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2010/060077

International filing date *(day/month/year)*
13 December 2010 (13.12.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
CHEN, Qi c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
CHEN, Qi 50 Forest Street Apt. 1710 Stamford, CT 06901 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 70 80	Authorized officer Malek David e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03

PATENT COOPERATION TREATY PCT/US2010/060077

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PCT

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1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
SU, Bao-Ning
c/o Bristol-Myers Squibb Company
1 Squibb Drive
New Brunswick, New Jersey 08903
United States of America

State of Nationality: CN
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
SU, Bao-Ning
14 Greyhound Court
Kendall Park, NJ 08824
United States of America

State of Nationality: CN
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Malek David
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03